Clinical Review Criteria
Drug-Eluting Stents for Coronary Revascularization

- Everolimus Eluting Stents
- Cordis’ Cypher Stent
- Cypher Sirolimus-Eluting Coronary Stent

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For Medicare Members

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For Non-Medicare Members
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Background
Percutaneous transluminal coronary angioplasty (PTCA) has become the preferred strategy for treating patients with blockage of one or more coronary arteries by atherosclerotic plaques. It is limited however, by the high rate of restenosis that may occur after a successful PTCA. The main processes involved in restenosis include the immediate elastic recoil of the vessel, rapid platelet deposition, late constrictive remodeling and neointimal hyperplasia. This problem stimulated the development of coronary endovascular stents which have been shown to reduce restenosis by preventing the elastic recoil and pathological remodeling. However, researchers found that stents do not prevent the restenosis caused by neointimal hyperplasia, but rather initiate an inflammatory reaction that induces more proliferation than other coronary devices (Surreys 2002).

An effective treatment of restenosis within the stent would be the suppression of neointimal hyperplasia. Investigators studied several modalities of treatment and pharmaceutical agents to inhibit restenosis after coronary interventions. Among these modalities is the local delivery of antiproliferative drugs via drug-coated stents. A drug-eluting stent (DES) is a device that releases single or multiple bioactive agents that can deposit in, or affect tissues adjacent to the stent. Potentially, it has the advantage of using a stent that is similar to that already in use, as well as delivering the drug in a high local concentration with no systemic toxic effects. Different stent designs with different immunosuppressive antimitotic agents including paclitaxel, rapamycin, actinomycin D, and tacrolimus have been developed by the device industry.

Currently two drug eluting stents are FDA approved and available for use; the sirolimus-eluting stent and the paclitaxel eluting stent. Both sirolimus and paclitaxel agents proved experimentally to be capable of significantly reducing or even inhibiting the intimal hyperplasia in animals and humans. Sirolimus is a macrolide antibiotic with a cytotoxic mechanism and an anti-inflammatory effect. The limus-family agents are active immunosuppressant and antiproliferative agents used to prevent graft rejection in kidney and heart transplantation (Hara 2006). They are...
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Evidence Conclusion: The trials reviewed had generally valid methodology with some limitations. However, all three trials included selected groups of patients that do not represent the real world patients with CHD that need intervention. Patients with multiple and/or complex coronary lesions were excluded from the trials as well as those at higher risk. The outcomes of the trials reviewed were short-term, and to date there is insufficient data on the long-term effects: benefits, limitations, or harms of the technology. The SIRIUS trial (Moses, 2003) showed that the target vessel failure (primary outcome) at 270 days of follow-up, was significantly lower among patients in the sirolimus stent group (8.6%) versus those in the standard stent group (21.0%) with an absolute risk reduction of 12.4%, and a number needed to treat of eight. The difference observed was mainly due to the higher target lesion thrombosis and potential fatal complications.

The RAVEL trial (Morice, 2002) conducted with sirolimus coated stents, showed that at six months, the angiographic rate of restenosis was 26% in the sirolimus stent group (8.6%) versus those in the standard stent group (21.0%) with an absolute risk reduction of 12.4%, and a number needed to treat of eight. The difference observed was mainly due to the higher target lesion thrombosis and potential fatal complications.

In April 2003, the Food and Drug Administration approved the first drug-eluting stent in the United States, the sirolimus-eluting CypherTM stent (Cordis, Johnson and Johnson CYPHER, Warren, NJ, USA) based on experience from the SIRIUS and RAVEL trials. One year later, in March 2004, the FDA approved the second drug eluting stent system, the Boston Scientific TAXUS™ Express2™ Paclitaxel-Eluting Coronary Stent System. The approved indications for the DES use were limited to the treatment of patients with symptomatic ischemic disease due to discrete de novo lesions <28 - <30 mm (<28 for Taxus, < 30 for Cypher) in length in native coronary arteries > 2.5 to < 3.75 mm in diameter. The FDA required that the manufacturers conduct a 2000-patient post-approval study and continue to evaluate patients enrolled in the original clinical trials for 5 years after implantation of the stent to assess its long-term safety and efficacy.

In July 2003, the manufacturer of the Cypher stent in conjunction with the FDA issued a warning letter to the US physicians on the risk of thrombosis that may occur at the time of implantation or within several days. More cases of thrombosis were observed with the use of the drug eluting stents, which led the FDA to convene a meeting of its Circulatory Systems Devices Panel in December 2006, to characterize the risk, timing, and incidence of DES thrombosis (FDA Update January 2007, Report of Advisory Panel, Laskey 2007).

DES was reviewed by MTAC in October 2003 and passed its evaluation criteria. The technology was also approved for coverage without criteria based on the evidence on its short term efficacy. At the time, there was a lack of long-term follow-up data.

Drug eluting stents are being re-reviewed by MTAC due to the concern regarding their long-term safety. Recent reports have suggested that the stents may be associated with an increased rate of the overall and late stent thrombosis and potential fatal complications.

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the standard stent group compared to none (0%) in the sirolimus stent group. At one year, 23% of the patients in the standard stent group needed repeat revascularization compared to none of those in the sirolimus group, with a number needed to treat of four. The results of TAXUS II trial (Colombo, 2003) using a different drug (paclitaxel) in their eluting stents, also showed significant reductions in restenosis and need for revascularization among patients in the drug-eluting stent group. Restenosis however was significantly reduced but not completely eliminated. In conclusion, the trials show that compared to the standard stents, the drug-eluting stents significantly reduced the rate of repeat revascularization at nine months to one year of follow-up, among the selected groups of patients included in the trials. They do not provide evidence on the long-term outcomes of the technology.

**Articles:** The search yielded 104 articles. Many were literature reviews and tutorials. There were eight articles on randomized controlled studies, three of which were different publications for the same trials. Two other RCTs compared drug eluting stents using the same coating drug but with different release velocities, and the others were smaller trials and/or with no clinically important outcomes. Few articles reported data on longer follow-up for subsets of population who received the drug-eluting stent with no control or comparison groups. The search also revealed few case series, with no control or comparison groups on subsets of patients treated for in-stent restenosis. SIRIUS (Moses, 2003) and RAVEL (Morice, 2002) trial using the Cypher Sirolimus-eluting stents were selected for critical appraisal. Another large trial (TAXUS II) using a different agent (Paclitaxel) for the drug-eluting stent was also selected for critical appraisal. All three RCTs compared the drug-eluting stents with the standard stents, and had clinically important outcomes. **Evidence tables were created for the following studies:** Moses JW, Leon MB, Popma JJ, et al. for the SIRIUS investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-1323. See Evidence Table. Morice M-C, Serruys PW, Sousa JE, et al for the RAVEL study group. A randomized comparison of a sirolimus-eluting stent for coronary revascularization. *N Engl J Med.* 2002;346:1773-1780. See Evidence Table. Colombo A, Drzewiecki J, Banning A, et al, for the TAXUS II Study Group. Randomized study to assess the effectiveness of slow and moderate release polymer-based paclitaxel-eluting stent for coronary artery lesions. *Circulation.* 2003;108:788-794. See Evidence Table.

The use of drug-eluting stents for coronary revascularization does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

**06/04/2007: MTAC REVIEW**

**Drug-Eluting Stents for Coronary Revascularization**

**Evidence Conclusion:** The results of the pivotal trials that led to the FDA stent approval (RAVEL, SIRIUS and TAXUS trials), showed significant reductions in the rate of stenosis and need for revascularization among the patients receiving drug-eluting stents whether sirolimus or paclitaxel coated. The trials however, were short-term and were neither designed nor powered to detect differences between the DES and bare metal stents in the rates of stent thrombosis and the associated MI and death. The technology was first reviewed by MTAC in October 2003. RAVEL and TAXUS II trials were included in the review, SIRIUS trials were not published then. This earlier review concluded that the results of the published trials at the time showed that compared to the standard bare-metal stents, the drug-eluting stents significantly reduced the rate of repeat revascularization at one year of follow-up, among the selected groups of patients included in the trials. It was noted however, that there was insufficient evidence to determine the long-term effects; benefits, limitations, or harms associated with the DES. The technology passed MTAC evaluation criteria, and is currently covered without criteria. It is being re-reviewed due to the publication of several reports suggesting that the stents may be associated with an increased rate of an overall and late stent thrombosis and potential fatal complications. This risk of stent thrombosis is the main safety concern in the current practice. However, it was not uniformly defined in the original trials. Moreover, it was not angiographically confirmed in many of the studies, and secondary stent thromboses occurring after revascularization were excluded in most trials. Some meta-analyses used the original definition of stent thrombosis in the protocol of the trials, while others redefined it or adopted the Academic Research Consortium (ARC) definition of stent thrombosis*. All these factors and others e.g. differences in the inclusion/exclusion criteria, make it difficult to pool the results for analysis and provide accurate comparisons of risks associated with the stents. Moreover, meta-analyses are conducted to combine moderate sized trials in order to provide sufficient statistical power. In this case, to determine the long-term efficacy and safety of the stents. Based on calculations performed by different investigators, the meta-analyses still lacked the sufficient power to detect significant associations between the DES and the long-term risk of myocardial infarction and mortality. Mauri and colleagues (2007) calculated that an RCT comparing two stents would require a sample size of approximately 8,000 patients to detect a doubling of the risk (from 1% to 2%) of stent thrombosis with 90% power. Spaulding et al (2007) reported that more than 11,000 patients are needed to provide sufficient power to detect a clinically significant difference in mortality. Holmes calculated a number of 4,621 per arm to reach a statistically significant difference in total mortality (211,053 for cardiac mortality) with 80% power. Some of these comparable and conflicting results of the meta-analyses are as follows. Sirolimus-eluting stents: In their meta-analysis of both sirolimus and paclitaxel DES, Stone and colleagues, 2007 (evidence table) pooled the results of 4 RCTs that compared the sirolimus-
eluting stents to bare metal stents (RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS, N= 1,748 participants). The SIRIUS trials included patients with de novo lesions of > 50% stenosis, 15-30 mm in length, in native coronary arteries 2.5-3.5 mm in diameter. The RAVEL study included patients with similar characteristics but with shorter blockages. In all trials patients with acute MI were excluded. The results of the analysis showed a significantly lower revascularization rate with the DES, but a higher rate of stent thrombosis (as defined in the study protocols) at 1-4 years with the sirolimus-eluting stents vs. bare metal stents with a NNH of 167. The meta-analysis did not show any difference between the stents in the cumulative rates of death or MI at 4 years. The latter might be due to the lack of power to detect a significant difference between the stents, or possibly because higher rates of MI or mortality were offset with the reduction in rate of complications associated with additional revascularization. It is worth noting that the authors of the meta-analysis had financial ties to the manufacturers of both drug eluting stents.

Spaulding et al, 2007 (evidence table), pooled the data for the same 4 RCTs on sirolimus eluting stents. The methodology of the analysis was valid, however the principal author also had financial ties to the manufacturer, and data for the individual studies were obtained from the manufacturer, which could lead to more accuracy or to bias. The results of the analysis showed that at 4 years, there were no statistically significant differences in the rates of death, MI, or stent thrombosis (as defined in the study protocols) between the two stent groups. When the authors of the meta-analysis used the ARC definition of stent thrombosis, they found a significantly higher rate for late (31 days-1 year) thrombosis with the bare metal stent (1.3% ) vs. sirolimus-eluting stent (0.3% , p=0.03). A subgroup analysis showed a higher mortality rate among patients with diabetes receiving a sirolimus-eluting stent vs. bare metal stent. Kastrati and colleagues (2007) performed a meta-analysis of 14 trials (N=4,958) that included the four pivotal trials, as well as ten other sirolimus trials with patient sizes ranging from 75-500. These additional trials included off-label use of the DES e.g. acute MI, venous bypass grafts, small vessels, long vessels, and complex lesions. A few of these trials were not published in peer-reviewed journals. The follow-up intervals ranged from 12.0-58.9 months, and the primary outcome of the meta-analysis was death from any cause. The pooled results of the analysis showed a sustained reduction in target lesion revascularization with the sirolimus stents, and no significant difference between the sirolimus and bare metal stents in the combined risk of death or MI, or stent thrombosis. However, after the first year of follow-up, the overall risk of stent thrombosis was significantly higher in the sirolimus vs. bare metal stent (0.6% vs. 0.02%, p=0.002). The author indicated that this was chronologically associated with the discontinuation of the dual antiplatelet therapy, according to the protocol specified duration. They however, did not make a statement but suggested the need for longer duration of dual antiplatelet therapy. In another meta-analysis of the same four pivotal sirolimus trials, Holmes and colleagues (2006), found no significant difference between patients receiving DES or bare metal stents in the rates of stent thrombosis or deaths related to it. They noted however that a sample size of 4, 621 per arm is required to provided sufficient power to detect a statistically significant difference in total mortality. Paclitaxel-eluting stents: Stone et al (2007) performed a separate analysis for paclitaxel eluting stents (evidence table). The results of their pooled analysis showed that paclitaxel drug eluting stents were associated with significantly less revascularization in the target lesion or target vessel (NNT for four years was 10 and 13 respectively). The results also indicate that the paclitaxel eluting stents were associated with a significantly higher rate of stent thrombosis between 1-4 years vs. the bare metal stent, with a NNH of 167 in 4 years. As regards MI and mortality rates, the only significant difference observed was the higher MI rate at more than 30 days to one year with the paclitaxel stent vs. bare metal stent. The results may only be generalized to patients with characteristics similar to the inclusion criteria of the trials included (on label use as defined by the FDA). Similar to the other meta-analyses on DES, the authors had financial ties to the manufacturers of both drug eluting stents. Ellis and colleagues 2007, conducted a meta-analysis of the Taxus II, IV, V, and VI (N=3,445) for up to 3 years of follow-up (3 years for TAXUS I & II, 2 years for TAXUS VI, and 1 year for TAXUS V). In the entire follow-up period, there was no significant difference in the cumulative stent thrombosis rate between the paclitaxel and bare metal stent. The TAXUS group however showed a statistically significant higher rate of stent thrombosis from 6 months to 3 years, vs. bare metal stent. Univariate and multivariate analysis showed that male gender, smoking, nonuse of clopidogrel, and possibly use of multiple non-overlapping stents were independently correlated to stent thrombosis. Meta-analyses that combined the results for both the sirolimus and paclitaxel-eluting stents: Mauri and colleagues 2007 pooled the follow-up data for the pivotal 4 sirolimus (RAVEL, and 3 SIRIUS trials, and four paclitaxel trials (Taxus I, II, IV and VI). The total number of participants was 4,545, and the median follow-up duration was 1,804 days for the sirolimus trials, and 1,426 days for the paclitaxel studies. In this meta-analysis the authors used pooled data on stent thrombosis based on the definition in the trials’ protocol, and according to the ARC, and found no increase in the stent thrombosis risk with either of the DES compared to the bare metal stent. They however noted that the power of the analysis was insufficient to detect statistically significant differences. Bavry et al (2006), performed a meta-analysis of 14 trials (N=6,675) that compared drug eluting stents (sirolimus and paclitaxel) to bare metal stents. The primary endpoint was angiographic stent thrombosis. However, those presumed by the trial investigators as stent thrombosis, without angiographic confirmations were also included. The results of the analysis showed no significant difference in the rates of early stent thrombosis. The incidence of very late stent thrombosis (> 1 year after the procedure) was 5.0 events/1000 patients receiving DES stents, compared to no events in the bare metal stents (RR=5.02, 95% CI 1.29-19.52, p=.02). Analyzed by the type of
DES, the relative risk was 3.99 (95% CI .45-35.62, p=.22) for the sirolimus stents, and 5.72 (95% CI 1.08-32.45, p=0.49 for the paclitaxel stents). It is to be noted however, that the SIRIUS and RAVEL trials enrolled half as many patients as the TAXUS trials. Nordmann et al (2006) conducted a meta-analysis of 17 trials with 8,221 participants (seven sirolimus trials n=2,487, nine paclitaxel trials n=4,908, and one on both n=826). The duration of follow-up was at least 1 year for all trials, was 2 years in 12 trials, 3 years for 9 trials, and 4 years for two trials. The pooled results of the meta-analysis showed no significant differences between the DES and bare metal stents in the total mortality rate. However, the rate of non-cardiac mortality at 2 years was significantly higher among patients randomized to the DES vs. bare metal stents. A subanalysis for each of the sirolimus and paclitaxel stents showed a significant difference associated with the sirolimus but not with the paclitaxel eluting stents when compared to the bare metal stents. The authors did not find a significant difference in the rate of stent thrombosis between the DES in general and the bare metal stents. The meta-analysis was well conducted; however the authors noted that the trials did not report on the rate of follow-up completion, and that there were no published data on cardiac and cardiac mortality for the TAXUS studies. The data analyzed were obtained from the manufacture. Moreno and colleagues (2007) conducted a meta-analysis of 25 RCTs (N=9,791) that compared DES to bare-metal stents to determine the risk of acute MI associated with each. They did not report on the quality of the trials included, how the patients were selected, and whether the studies were randomized and blinded. The results of the pooled analysis showed that the DES were associated with a decreased need for subsequent revascularization as well as a decreased incidence of acute myocardial infarction in the first 12 months after stent implantation. The authors noted that this could be due to a decrease in the incidence of non-Q-wave acute myocardial infarction. A subanalysis showed an odds ratio of 1.20 (95% CI 0.65-20.2) for Q wave MI, and 0.79 (95% CI 0.60-1.06) for non Q-wave MI. The authors did not analyze data on stent thrombosis, nor did they evaluate the effect of very late thrombosis on the risk of MI. Comparison between the Sirolimus and paclitaxel stents: The REALITY trial (Morice 2006) compared the safety and efficacy of sirolimus-eluting vs. paclitaxel-eluting coronary stents. The trial randomized 1,386 patients with angina, and 1 or 2 de novo lesions in native arteries (2.25-3.00 mm in diameter) from 90 hospitals in Europe, Latin America, and Asia, to receive one of the two DES. The primary outcome was in-lesion binary stenosis (stenosis >50% of the luminal diameter) confirmed angiographically at 8 months. The secondary outcome was the rate revascularization and composite endpoint of cardiac death, MI (Q-or non-Q wave), and CABG surgery or repeat target revascularization at 12 months. The authors concluded that the results of the trial showed no difference between the two DES in the rate of binary stenosis or major adverse cardiac events. The trial was powered to prove there is no difference in rate of restenosis but not to detect equivalence between the stents in the event rates. Off-label use: Two more recently published observational studies (Win et al, 2007 and Boehar et al, 2007) assessed the effectiveness and safety of DES for off-label use and untested indications. The studies were relatively large but were only observational, with no control group, and only 12 months of follow-up. These observational studies may only show if there is an association but cannot determine if it is causal. The analysis of the results of these studies indicated that the off-label and untested use of the DES was associated with higher rate of stent thrombosis and adverse outcomes. Dual antiplatelet therapy: Basal Stent Kosten Effektivitata Trial (BASKET) was a randomized controlled trial (N=826) conducted in Switzerland to compare the 6-month clinical outcomes and cost effectiveness of the sirolimus and paclitaxel-eluting stents versus the bare metal stents. It included on/off label use of the DES. The BASKET-LATE (Pfisterer, 2006), was an observational study that followed-up a series of 746 patients (with 1,133 stented lesions) from BASKET, who survived 6 months without major events (nonfatal MI, or repeat revascularization) for one year after the discontinuation of clopidogrel. The primary outcome was cardiac death and MI. The results of this observational study suggest that after discontinuation of clopidogrel (between 7 and 18 months after implantation) the rates of cardiac death and MI were higher with the drug eluting stents than with bare metal stents (4.9% vs. 1.3% respectively). Thrombosis related events (88% MI or death) occurred between 15 and 362 days after the discontinuation of clopidogrel. Conclusion: The results of the published meta-analyses are conflicting in many cases, even for those that pooled the results for the same trials. This could be attributed to different definitions used by the investigators for stent thrombosis, the inclusion and exclusion criteria of the meta-analyses, differences in the clinical protocols of the studies, characteristics of patients and their lesions, and/or different approaches used to analyze the same data. The overall results of these analyses indicate that DESs are associated with a significant decrease in the need for revascularization after the implantation of the stent. They also point towards an increased risk of late stent thrombosis with the drug eluting stents. The analyses do not provide sufficient power to determine if this stent thrombosis is associated with increased risk of acute myocardial infarction and/or mortality. There are also insufficient data to determine if this late stent thrombosis could be attributed to the early discontinuation of antiplatelet therapy. The evidence on the optimal duration of antiplatelet therapy after the placement of a DES is lacking as well. Findings from non-randomized studies suggest a relation between late stent thrombosis and discontinuation of dual antiplatelet therapy, and suggest more prolonged course of clopidogrel than that recommended by the stent manufacturers (3 months for Cypher, and 6 months for Taxus stents). The current U.S. and European guidelines, as well the as the Circulatory Systems Devices Advisory Panel for the FDA recommend that antiplatelet therapy be taken for at least 12 months unless a patient is at high risk for bleeding.

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**Articles:** The search revealed more than 1,000 articles published after our first review. These included over thirty meta-analyses comparing the drug eluting stents vs. the bare metal-stents, or comparing different stents with one another for on and/ or off-label use of the stents. There were also published reports from national registries that recorded long-term data on patients receiving the drug-eluting stents for on and off-label indications.

This report will focus on reviewing meta-analyses of randomized controlled trials rather than individual trials. In order to select those with the most valid methodology for critical appraisal, the published met-analyses were screened to determine whether: The authors conducted a systematic literature search, and addressed possible publication bias; The authors stated the inclusion and exclusion criteria for studies they included in the analysis; Selection of the trials and interpretation of the data were conducted by more than one investigator; The quality of the studies was evaluated, and a quality scores given to each study included; The results were pooled and data interpreted with appropriate statistical methods; Data were published in peer reviewed journals or obtained from manufacturers’ database; The meta-analysis was conducted by the manufacturer or by independent experts. Screening the published meta-analyses based on these criteria showed that there was no perfect one that fulfilled all criteria. Some included only the pivotal trials that had specific inclusion criteria and resulted in approval of the DES by the regulatory agencies in United States and Europe. Others performed systematic literature searches and included larger numbers of studies, but did not indicate if they were of good quality and if the stent use was on /off label use in trials included. The inclusion criteria for the individual studies varied and were not provided in the majority of the meta-analyses, neither were the rates of on /off-label use of the DES. Some authors combined the results for the sirolimus and paclitaxel-eluting stents compared to bare-metal stents; others restricted their analyses to one of the two DES. The long-term follow-up data were mainly obtained from the manufacturers’ databases. The rates of follow-up as well as the duration of antiplatelet therapy used after stenting were not provided. The authors of many of these meta-analyses had financial ties to the manufacturers. Two of the meta-analyses were selected for presentation in evidence tables to demonstrate how pooling data for the same trials could lead to different results due to differences in defining thrombosis and/or using different approaches in the analysis. These two meta-analyses, as well as seven others are also presented in a table form (attached), and in the reviewer’s summary section of this report. *The following meta-analyses are presented in evidence tables:* Stone GW, Moses J W, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998-1008. See Evidence Table. Spaulding C, Daemen J, Boersma E, et al. A pooled analysis of data comparing of sirolimus- eluting stents with bare-metal stents. N Engl J Med 2007;356:989-997. See Evidence Table.

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