



# CIGNA MEDICAL COVERAGE POLICY

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**Subject Drug-Eluting Stents for Ischemic Heart Disease**

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## Hyperlink to Related Coverage Policies

Coronary Artery Brachytherapy  
Excimer Laser Coronary Angioplasty

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## Coverage Policy

**CIGNA covers the use of drug-eluting stents as medically necessary for the treatment of symptomatic ischemic heart disease due to de novo lesions in native coronary arteries (with the exception of unprotected left main coronary artery disease) or stenosis within a previously placed bare-metal stent.**

**CIGNA does not cover drug-eluting stents for any other indication, including treatment of saphenous vein graft disease, because it is considered experimental, investigational, or unproven.**

## General Background

Coronary artery disease is a leading cause of morbidity and mortality in the United States. It is caused by stenosis of coronary arteries as a result of deposits of atherosclerotic plaque. Coronary artery stenosis may be asymptomatic, or it may cause angina of varying degrees. Severe reduction in the circulation to the heart may cause myocardial infarction (MI) that can lead to death. Symptoms and health risks of coronary artery stenosis may be treated medically by modifying risk factors and/or by administering medications such as beta blockers, calcium channel blockers, nitrates, statins, and antiplatelet agents. When medical treatment is not effective or is not appropriate, percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) are considered.

PTCA, introduced in the 1970s, is a minimally-invasive procedure in which a catheter with an inflatable balloon at the tip is inserted into the lumen of the artery and inflated, dilating the area of blockage. Percutaneous

coronary intervention (PCI) is a broader term that encompasses PTCA and various other techniques introduced to relieve coronary narrowing. Atherectomy, brachytherapy, and implantation of coronary stents are interventions that fall within the broader category of PCI techniques. Restenosis following PCI with stenting is common; approximately 15–20% of stented arteries restenose, requiring repeat revascularization procedures. Drug-eluting stents (DES) were developed to address the problem of restenosis.

Although long-term studies have not demonstrated a significant effect on rates of death or MI with DES, there is evidence that DES result in a lower rate of repeat revascularization compared to bare metal stents. Inclusion criteria for trials that formed the basis for U.S. Food and Drug Administration (FDA) approval evaluated DES in patients with relatively uncomplicated disease. The use of DES expanded widely since their introduction; in 2003; in 2005, the use of DES as a percentage of all percutaneous coronary intervention (PCI) procedures peaked at close to 90%. The use of DES decreased to 63% of PCI procedures during 2006–2007, following publication of data regarding late in-stent thrombosis and increasing awareness of the need for long-term dual antiplatelet therapy. Data from the last quarter of 2008 indicated DES were used in 68% of all PCI procedures (Epstein et al., 2011)

DES are frequently employed beyond the limits of their approved indications for use. There is adequate evidence that DES may be appropriate for expanded indications, including recent myocardial infarction (MI), complex disease (i.e., small vessels, long lesions, multi-vessel disease), and in-stent restenosis. The use of DES has also been proposed for treatment of unprotected left main coronary artery disease (LMCA) and saphenous vein graft (SVG) disease. There is insufficient evidence in the published medical literature, however, to demonstrate safety and efficacy of DES for these indications.

#### **U.S. Food and Drug Administration (FDA)**

##### **CYPHER™ Sirolimus-Eluting Coronary Stent on the RAPTOR™ Over-the-Wire Delivery System or RAPTORRAIL® Rapid Exchange Delivery System (Cordis Corp., Miami Lakes, FL)**

The CYPHER™ sirolimus-eluting stent received premarket approval (PMA) from the U.S. Food and Drug Administration in April 2003 for patients with symptomatic ischemic disease due to discrete de novo lesions of up to 30 mm in length with a reference vessel diameter of 2.5–3.5 mm. The safety and efficacy of this stent had not yet been demonstrated for use in vessels smaller than 2.5 mm or for bifurcating lesions, chronic total occlusions, saphenous vein graft disease, failure of vascular brachytherapy, lesions in the left main coronary artery, multivessel disease, in-stent restenosis, or in patients with acute MI.

Sirolimus (rapamycin) was approved by the FDA in 1999 as an anti-rejection drug to be used following organ transplantation. The Cordis CYPHER sirolimus-eluting stent is a stainless steel balloon-expandable stent coated with a mixture of synthetic polymers and sirolimus. A second coat of drug-free polymers is then applied to the stent as a diffusion barrier to prolong the release of the drug. The design allows 80% of the drug to be released within 30 days of implantation. FDA approval was based largely on the results of two clinical studies: the RAVEL trial and the SIRIUS trial.

##### **TAXUS™ Express 2™ Paclitaxel-Eluting Coronary Stent System (Monorail and Over-the-Wire)(Boston Scientific Corp., Natick, MA)**

The TAXUS Express paclitaxel-eluting stent (PES) system received U.S. FDA approval in March 2004 through the PMA process. The TAXUS stent was approved for the treatment of de novo lesions of less than 28 mm in length in native coronary arteries from 2.5–3.75 mm in diameter. FDA approval was based in large part on the results of the TAXUS-IV trial, which demonstrated results comparable to the sirolimus-eluting stents (SES) in inhibiting connective tissue and smooth muscle proliferation. Paclitaxel acts by halting inflammation mediators and interrupting cell migration and proliferation.

##### **Endeavor® Zotarolimus-Eluting Coronary Stent on the Over-the-Wire (OTW), Rapid Exchange (RX), or Multi Exchange II (MX2) Stent Delivery Systems (Medtronic Vascular, Santa Rosa, CA)**

The Endeavor® Zotarolimus-Eluting Coronary Stent received U.S. FDA approval through the PMA process on February 1, 2008. According to the approval order, the Endeavor stent is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to de novo lesions of length  $\leq 27$  mm in native coronary arteries with reference vessel diameters of  $\geq 2.5$  mm to  $\leq 3.5$  mm. The drug component of the Endeavor stent consists of zotarolimus (the active ingredient) and Phosphorylcholine polymer (the inactive ingredient). Zotarolimus is a tetrazole-containing macrocyclic immunosuppressant. The safety and efficacy information was obtained primarily from the ENDEAVOR trials (I, II, III, and IV).

### **XIENCE™ V Rapid-Exchange (RX) Everolimus Eluting Coronary Stent on the Over-the-Wire (OTW) or Rapid Exchange (RX) Stent Delivery Systems (Abbott Vascular, Santa Clara, CA)**

The XIENCE V Everolimus Eluting Coronary Stent System received FDA approval through the PMA process on July 2, 2008. The approval order states that the XIENCE stent is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to de novo native coronary artery lesions (length  $\leq$  28 mm) with reference vessel diameter of 2.5 mm to 4.25 mm. The system consists of two components; a MULTI-LINK VISION® Coronary Stent System or MULTI-LINK MINI VISION® Coronary Stent System, and a drug coating (formulation of everolimus in a polymer coating). FDA approval was based primarily on safety and effectiveness information from the SPIRIT III trial.

#### **Literature Review**

**Cordis CYPHER™ Sirolimus-Eluting Stent:** The RAVEL (RAnomised study with the Sirolimus coated BX™ VELOCITY balloon expandable stent (CYPHER) in the treatment of patients with de novo native coronary artery Lesions) trial was a European multicenter randomized, double-blind trial involving 238 patients. The trial compared sirolimus-eluting stents (SES) with standard bare metal stents for revascularization of single, primary lesions in native coronary arteries. At six months, the SES group had statistically significant lower restenosis rates than the standard stent group. In addition, at one year the SES group had a statistically significant difference in the rate of major cardiac events (5.8% vs. 28.8%) than the standard stent group (Morice, et al., 2002). The one-, three-, and five-year rates of survival free of target lesion revascularization (TLR) were 99.2%, 93.8%, and 89.7%, respectively, in the SES group, and 75.9%, 93.8%, and 89.7%, respectively, in the BMS group. Major adverse cardiac event (MACE) rates at five years were 25.8% in the SES group compared to 35.2% in the BMS group ( $p=0.03$ ). Rates of stent thrombosis were similar in both groups.

SIRIUS (SIRollmUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions), a multicenter, randomized, double-blind trial compared SES with standard stents, and demonstrated the consistent treatment effect of the SES even in patients with complex coronary lesions, with a failure rate of 8.6% vs. 21% with a standard stent. The low failure rate was based primarily on the reduced frequency of the need for revascularization in the SES group—4.1% vs. 16.6% in the standard stent group (Moses, et al., 2003).

**TAXUS Express Paclitaxel-Eluting Stent (PES):** The TAXUS-IV trial was a prospective, randomized, double-blind trial that demonstrated significant reduction in restenosis for patients who received the paclitaxel-eluting stent (PES). The trial included 1314 patients at 73 U.S. centers receiving a stent in a single, previously untreated stenosed coronary artery with a vessel diameter of 2.5–3.75 mm, lesion length 10–28 mm. Patients were randomly assigned to receive either a BMS or a slow-release, polymer-based, PES. Seven hundred thirty-two patients were assigned to receive angiographic follow-up after nine months. Angiographic restenosis in the paclitaxel-eluting stent group was 7.9% as compared to 26.6% in the group receiving bare metal stents. The rate of ischemia-driven TVR was 4.7% in the PES group vs. 12% of the bare metal stent group (Stone, et al., 2004).

This study did not establish the safety and efficacy of PES in patients with lesions resulting from acute MI, thrombus-containing lesions, bifurcations, stenoses of the left main coronary artery, heavily calcified stenoses, vessels estimated at less than 2.5 mm or greater than 3.75 mm in diameter, diseased saphenous-vein grafts, or lesions with in-stent restenoses. Patients with any of these lesions were excluded from the trial.

**Endeavor® Zotarolimus-Eluting Coronary Stent on the OTW, RX, or MX2 Stent Delivery Systems:** The Endeavor zotarolimus-eluting stent (ZES) received FDA approval based primarily on the results of ENDEAVOR I, II, III, and IV ENDEAVOR II, a prospective, randomized, double-blind study ( $n=1197$ ) conducted by Fajadet, et al., for the Endeavor II Investigators (2006), compared the Endeavor ZES to a control BMS. Patients treated for single coronary artery stenosis were randomized to the Endeavor ZES ( $n=598$ ) or the same BMS without the drug or polymer coating ( $n=599$ ). The primary endpoint, target vessel failure at nine months, was 7.9% with the Endeavor stent, compared to 15.1% with the BMS ( $p=0.0001$ ). The MACE rates and TLR rates were also lower in the Endeavor group (7.3% and 4.6%, respectively), compared to the BMS group (14.4% and 11.8%, respectively) ( $p=0.0001$ ). There was no significant difference in the rate of stent thrombosis. Angiographic follow-up demonstrated reduced rates of in-segment and in-stent late loss in the Endeavor group compared to the BMS group ( $p<0.001$ ), as well as lower rates of in-segment restenosis ( $p<0.0001$ ). Differences in clinical outcomes were maintained at 9, 12, and 24 months ( $p<0.0001$ ).

ENDEAVOR III (Kandzari, et al., for the ENDEAVOR III Investigators, 2006) was a randomized, controlled, single-blinded trial designed to compare the safety and efficacy of the Endeavor zotarolimus-eluting stent (ZES) to the Cypher sirolimus eluting stent (SES) at 29 hospitals in the U.S. A total of 436 patients undergoing elective percutaneous coronary revascularization were randomized to ZES (n=323) or SES (n=113). Eight-month angiographic in-segment late lumen loss, the primary endpoint, was significantly higher in the ZES group compared to the SES group ( $0.34 \pm 0.44$  vs.  $0.13 \pm 0.32$ , respectively;  $p < 0.001$ ). In-segment binary angiographic restenosis was also higher in the ZES group compared to the SES group (11.7% vs. 4.3%,  $p = 0.04$ ). In-hospital MACE rates, however, were significantly lower in the ZES group compared to the SES group (0.6% vs. 3.5%,  $p = 0.04$ ). There was no significant difference in rates of clinically driven TLR or target vessel failure.

Gershlick et al., for the ENDEAVOR Investigators (2007) conducted a systematic analysis of pooled clinical and angiographic outcomes in 1317 patients treated in the first four Endeavor trials, Endeavor I, II, II CA, and III. Follow-up angiography was performed in a subset of 750 patients at eight or twelve months post-procedure. Clinical follow-up was conducted nine months after the procedure in all patients. Diabetes was present in 22.5% of patients. The overall rate of stent thrombosis at 24 months was 0.3%, and no events occurred > 14 days following the procedure. Although varied clinical and angiographic characteristics were observed, ZES were associated with consistently low rates of TLR and overall MACE, including stent thrombosis. The authors stated that ongoing study with more open inclusion criteria will be important to determine whether comparable clinical outcomes can be extended to more complex lesions.

Leon et al. (2011) published three-year follow-up of ENDEAVOR IV, a randomized single blind study comparing the zotarolimus-eluting stents (ZES) with paclitaxel-eluting stents (PES) in 1548 patients with de-novo native coronary artery lesions. ZES compared to PES reduced target vessel failure, myocardial infarction (MI), and cardiac death plus MI. The overall rate of stent thrombosis did not differ significantly at three years, but very late stent thrombosis (i.e., 1–3 years) was reduced significantly in ZES patients. Ischemia-driven target lesion revascularization at three years was similar in both groups.

**XIENCE V Everolimus Eluting Coronary Stent System:** The SPIRIT III trial, a prospective, randomized, single-blind, controlled trial, compared the safety of the XIENCE V everolimus eluting-stent (EES) to the Taxus Express 2 PES (Stone, et al., 2008). Patients with one or two de novo lesions in native coronary arteries were randomized in a 2:1 ratio to the XIENCE V stent (n=669) or the Taxus 2 stent (n=333). Lesions were  $\leq 28$  mm in length with reference vessel diameter between 2.5 and 3.75 mm. Angiographic follow-up was pre-specified in 564 patients at eight months, and was completed in 436 patients. The primary end point was non-inferiority or superiority of angiographic in-segment late loss. There was significantly less in-segment late loss in the EES group compared to the PES group ( $p \leq .001$ ). The EES was non-inferior to the PES for target vessel failure at nine months ( $p < .001$ ). The EES compared to the PES resulted in significant reductions in composite MACE at nine months ( $p < .03$ ) and at one year ( $p = .02$ ).

Stone et al. published two year outcomes of the Spirit III trial in 2009. Clinical follow-up at two years was available for 951 (94.9%) patients. Between one and two years, patients treated with EES compared to PES tended to have fewer episodes of stent thrombosis (0.2% vs. 1.0 %,  $p = 0.10$ ), and MI (0.5% vs. 1.7%;  $p = 0.12$ ). At two years, treatment with EES compared to PES resulted in a 32% reduction in target vessel failure (10.7% vs. 15.4%;  $p = 0.04$ ); and a 45% reduction in MACE (7.3% vs. 12.8%;  $p = 0.004$ ). A total of 360 patients discontinued clopidogrel or ticlopidine after six months. In these patients, there was a trend toward fewer stent thrombosis events in the EES patients (0.4%) compared to the PES patients (2.6%) ( $p = 0.10$ ).

### Expanded Indications

Research is ongoing in the application of drug-eluting stents for expanded indications, including use in patients with acute MI, complex coronary artery disease (CAD), in-stent restenosis, unprotected left main coronary artery disease, and saphenous vein graft disease.

**Acute MI:** Laarman et al. (2006) evaluated the use of PES compared to an uncoated stent in patients undergoing PCI for acute MI with ST-segment elevation (n=619). Patients were randomized to a PES (n=310) or an uncoated stent (n=309). The primary endpoint was a composite of death from cardiac causes, recurrent MI, or target-lesion revascularization at one year. Although the use of a PES reduced the incidence of serious adverse cardiac events at one year by four percentage points as compared to uncoated stents, the difference

was not statistically significant. The incidence of stent thrombosis during follow-up was the same in both groups at 1%.

Results of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction With ST Segment Elevation) trial (Vink et al., 2011) demonstrated comparable rates of cardiac death, recurrent MI, or target lesion revascularization at five years in patients randomized to PES (n=310) or BMS (n=309). The incidence of stent thrombosis was not significantly different in the PES group compared to the BMS group (4.2% vs. 3.4%, respectively), although very late stent thrombosis was seen almost exclusively in the PES group.

Menichelli et al. (2007) conducted a randomized controlled trial (n=320), Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI), to evaluate the incidence of restenosis in patients with STEMI treated with SES vs. BMS. At one year, the incidence of binary restenosis was lower in the SES group than in the BMS group (9.3% vs. 11.2%, p=0.02). Rates of TLR, major adverse cardiac events (MACE), and target vessel failure were also lower in the SES group vs. the BMS group (5% vs. 13.1%, p=0.015; 6.8% vs. 16.8%, p=0.005; 8.7% vs. 18.7%; p=0.007; respectively). A three year follow-up to the SESAMI trial (Violini et al, 2009) demonstrated a lower incidence of MACE in the SES group compared to the BMS group (12.7 % vs. 21%, p=0.034), as well as lower rates of target lesion revascularization (7% vs. 13%, p=0.048), target vessel revascularization (8% vs. 16%, p=0.027), and target vessel failure (11.5% vs. 20.5%, p=0.028). The lower incidence of adverse events was driven by the reduced target lesion revascularization rates and was achieved in the first year of follow-up. Four-year follow-up of TYPHOON (Trial to Assess the Use of the Cypher Sirolimus-eluting Coronary Stent in Acute Myocardial Infarction (Spaulding et al., 2011).also demonstrated sustained efficacy of SES in reducing target lesion revascularization, with no difference in death, repeat MI or stent thrombosis.

Kastrati et al. (2007) conducted a meta-analysis of eight randomized trials of DES (sirolimus or paclitaxel) vs. BMS in patients with acute MI. Individual data were available for seven trials (476 patients). Patients were followed for a mean of 12.0–24.2 months. The primary endpoint was the need for reintervention (target lesion revascularization). The primary safety endpoint was stent thrombosis. DES significantly reduced the need for reintervention (p<0.001). There was no significant difference between DES and BMS in the overall risk of stent thrombosis (p=0.43), death (p=0.14), or recurrent MI p=0.11). Pasteri et al. (2007) conducted a similar meta-analysis that included six of the seven trials in the Kastrati analysis, also concluding that the use of DES reduces the risk of revascularization, without changes in the incidence of death, MI, or stent thrombosis at one-year follow-up.

De Luca et al. (2009) conducted a meta-analysis of 11 randomized trials of DES in ST-segment elevation myocardial infarction (STEMI). Of 3605 patients, 1888 (52.3%) were randomized to DES, and 1719 (47.7%) were randomized to BMS. At 12 months, there was no significant difference between DES and BMS in mortality (4.1% vs. 4.4%, p=0.59), reinfarction (3.1% vs. 3.4%, p=0.38), or stent thrombosis (1.6% vs. 2.2%, p=0.22). DES were associated with a significant reduction in TVR, however (5.0% vs. 12.6%, p<0.0001).

Evidence published to date indicates the use of DES in STEMI results in similar rates of recurrent MI, stent thrombosis, and death compared to BMS, with lower rates of revascularization. Most studies include relatively short follow-up, however. DES may be considered as an alternative to a BMS for primary PCI in STEMI. Additional evidence from large randomized trails with longer follow-up will further define the role of DES in STEMI.

**Complex Coronary Artery Disease (Small Vessels, Long Lesions, Multi-Vessel Disease):** Pivotal randomized trials of DES restricted enrollment to relatively simple stenoses. Several studies have evaluated the safety and efficacy of DES in patients with more complex lesions than those previously studied.

The treatment of lesions in small coronary arteries is problematic. Revascularization by CABG is technically difficult and is associated with high failure and mortality rates, while revascularization by standard balloon angioplasty and stent implantation is associated with high complication and restenosis rates. It has been proposed that DES may effectively prevent restenosis in small coronary arteries. Schofer et al. (2003) conducted a double-blind randomized controlled trial (n=352) to compare the use of sirolimus-eluting stents (SES) with bare metal stents (BMS) in long atherosclerotic lesions in small coronary arteries (diameter 2.5–3.0 mm, lesion length 15–32 mm). Patients were randomly assigned to receive an SES (n=175) or BMS (n=177). At eight months, minimum lumen diameter was higher in the SES group (2.22) than in the BMS group (1.33 mm),

and binary restenosis was significantly reduced in the SES group (5.9%) compared to the BMS group (42.3%). The MACE rate at nine months was lower in the SES group (8.0%) compared to the BMS group (22.6%), due largely to a lower rate of TVR.

The TAXUS V trial (Stone, et al., for the TAXUS V investigators, 2005), a placebo-controlled, double-blind, multicenter randomized trial, evaluated the safety and efficacy of the paclitaxel-eluting stent (PES) in 1156 patients who underwent stent implantation in a single coronary artery stenosis (vessel diameter, 2.25–4.0 mm; lesion length, 10–46 mm), including 664 patients (57.4%) with complex or previously unstudied lesions requiring 2.25 mm, 4.0 mm, and/or multiple stents. Patients were randomly assigned to receive one or more BMS (n=579) or identical-appearing PES (n=577). Compared with BMS, PES reduced the nine-month rate of target lesion revascularization from 15.7% to 8.6% and target vessel revascularization from 17.3% to 12.1%. Similar rates were observed for cardiac death or MI, at 5.5% in the BMS group vs. 5.7% for the PES group. The rate of stent thrombosis was 0.7% in both groups. Angiographic restenosis was reduced from 33.9% to 18.9% in the study group, including patients treated with 2.25 mm stents (49.4% vs. 31.0%) and 4.0 mm stents (14.4% vs. 3.5%), and multiple stents (57.8% vs. 27.2%). The authors concluded that, compared with a BMS, implantation of the PES in a patient population with complex lesions effectively reduces clinical and angiographic restenosis.

The TAXUS VI trial (Dawkins, et al., on behalf of the TAXUS VI Investigators, 2005), a multicenter, double-blind, randomized trial, assessed clinical and angiographic outcomes of the TAXUS stent in the treatment of long, complex coronary artery lesions (n=448). Patients were randomized to receive a moderate-release (MR) TAXUS Express stent or an uncoated Express control stent. At the time, only slow-release TAXUS stents were commercially available. At nine months, target vessel revascularization was 9.1% in the TAXUS group and 19.4% in the control group. Target lesion revascularization was reduced from 18.9% to 6.8% respectively. The incidence of MACE was similar in both groups at 16.4% in the TAXUS group and 22.5% in the control group, including comparable rates of acute MI. Binary restenosis in the stented area was reduced from 32.9% in the control group to 9.1% in the TAXUS group. The authors concluded that the finding that the TAXUS MR stent system is safe and effective in the treatment of long, complex coronary lesions provides evidence for the more widespread use of drug-eluting stents in contemporary clinical practice.

The use of DES has evolved as an alternative to coronary artery bypass graft (CABG) surgery in patients with multivessel disease. Arterial Revascularization Therapies Study (ARTS) was a randomized multicenter trial comparing surgery (CABG) with bare metal stents (BMS) in patients with multivessel disease. Arterial Revascularization Therapies Study Part II (ARTS II) trial (Serruys et al., 2010), a multicenter observational study, compared five-year clinical outcomes, safety, and efficacy of SES in ARTS II with the outcomes of CABG and bare metal stenting from ARTS I. The death/stroke/myocardial infarction event-free survival rate was 87.1% in ARTS II SES vs. 86.0% in ARTS I CABG (p=0.1) and 81.9% in ARTS I BMS (p=0.007). The five-year major adverse cardiac and cerebrovascular event (MACCE) rate in ARTS II was significantly higher (27.5%) than ARTS I CABG (21.1%, p=0.02) and lower than in ARTS I BMS (41.5%, p <0.001). The cumulative incidence of stent thrombosis was 3.8%. Of 176 major adverse cardiac events (MACE) 56 (32%) were related to possible, probable or definite stent thrombosis.

Drug-eluting stents (DES) have become widely used in clinical practice, expanding beyond treatment of the simple lesions evaluated in early pivotal clinical trials. Several well-designed, randomized controlled clinical trials described above have established the safety and efficacy of DES in the treatment of more complex lesions in patients with suitable anatomy and clinical presentation.

**In-Stent Restenosis:** Outcomes of treatment of in-stent restenosis with currently available interventional methods such as balloon angioplasty, repeated use of bare metal stents (BMS), atherectomy and excimer laser angioplasty have been disappointing. Coronary artery brachytherapy has demonstrated greater efficacy, but the procedure is complex, and the long-term effects of intracoronary radiation are not known. DES have been used as an alternative treatment of in-stent restenosis.

The TAXUS V ISR trial (Stone, et al., for the TAXUS V ISR Investigators, 2006), a multicenter randomized trial (n=396), evaluated the safety and efficacy of the PES vs. brachytherapy in the treatment of patients with restenotic lesions after prior stent implantation in native coronary arteries. Patients were randomly assigned to angioplasty followed by vascular brachytherapy (n=201) or PES implantation (n=195). Follow-up at nine months was complete in 194 patients in the brachytherapy group and 191 patients in the DES group. For brachytherapy and PES, respectively, the number of events and nine-month rates for ischemic target lesion revascularization

were 27 (13.9%) vs. 12 (6.3%); for ischemic target vessel revascularization, 34 (17.5%) vs. 20 (10.5%); and for overall MACE, 39 (20.1%) vs. 22 (11.5%), with similar rates of cardiac death or MI and target vessel thrombosis. Angiographic restenosis at nine months was 31.2% (53 of 170 patients) with brachytherapy and 14.5% (25 of 172 patients) with PES. The authors concluded that treatment of BMS in-stent restenotic lesions with PES rather than angioplasty followed by brachytherapy reduces clinical and angiographic restenosis at nine months and improves event-free survival.

A randomized multicenter trial (Holmes, et al. for the SISR Investigators, 2006) evaluated the safety and efficacy of the sirolimus-eluting (SES) compared with vascular brachytherapy for the treatment of patients with restenosis within a BMS (n=384). Patients were randomized to vascular brachytherapy (n=125) or SES (n=259). The rate of target vessel failure was 21.6% (27/125) with brachytherapy and 12.4% (32/259) with SES. Target lesion revascularization was required in 19.2% (24/125) of the brachytherapy group and 8.5% (22/259) of the SES group. The rate of binary angiographic restenosis was 29.5% (31/105) for the brachytherapy group and 19.8% (45/227) for the SES group. Minimal lumen diameter was larger in the SES group at six-month follow-up than in the brachytherapy group, reflecting greater net lumen gain. The authors concluded that SES result in superior clinical and angiographic outcomes compared with vascular brachytherapy for the treatment of restenosis within a BMS.

Dibra et al. (2007) conducted a meta-analysis of randomized trials to synthesize the available evidence on the effectiveness of DES for treatment of BMS in-stent restenosis. Four randomized studies comparing SES or PES vs. balloon angioplasty or vascular brachytherapy in 1230 patients were evaluated. The risk of target lesion revascularization and angiographic restenosis were markedly lower in patients treated with DES. There was no difference in the composite of death or MI between patients treated with DES and those treated with other techniques.

In-stent restenosis following PCI is a significant clinical problem, frequently resulting in the need for repeat revascularization procedures. Coronary artery brachytherapy has been the only available treatment shown to be effective for BMS restenosis, but questions remain as to the safety of ionizing radiation for the treatment of vascular lesions. Although additional follow-up is needed to evaluate long-term efficacy and outcomes, DES have been shown in well-designed trials to provide improved clinical and angiographic outcomes in the treatment of restenosis within a BMS when compared to brachytherapy.

**Unprotected Left Main Coronary Artery Disease:** Unprotected left main coronary artery (LMCA) disease is disease in the left main coronary artery that is not “protected” by a patent bypass graft to the left anterior descending or circumflex artery. Lesions in the unprotected LMCA (are one of the most challenging subsets in percutaneous coronary intervention (PCI) and are generally treated by surgical revascularization. The use of DES has been explored as an alternative to coronary artery bypass graft (CABG) surgery in the treatment of unprotected LMCA disease.

Biondi-Zoccai et al. (2008) conducted a systematic review and meta-analysis to review outcomes of DES implantation in unprotected LMCA disease, and to compare these outcomes with PCI using BMS and to CABG. The primary end-point was MACE (i.e., death, MI, or TVR) at the longest follow-up. The analysis included 16 studies (1278 patients), with a median follow-up of ten months. Meta-analysis showed a MACE rate of 16.5% (11.7%–21.3%); death rate of 5.5% (3.4%–7.7%); and TVR rate of 6.5% (3.7%–9.2%). Comparison of DES vs. BMS demonstrated adjusted odds ratios for MACE of 0.34 (0.16–0.71), and DES vs. CABG showed adjusted odds ratios for MACE plus stroke of 0.46 (0.24–0.90). The authors stated that although clinical studies report apparently favorable early and midterm results in selected patients with unprotected LMCA disease, but noted the limitations in validity of studies due to statistical inconsistency, differences in patients and techniques, and lack of data on MACE for the PCI vs. CABG comparison. The authors concluded that results from randomized controlled trials are needed to definitely establish the role of DES as compared to the reference treatment, surgery.

Park et al. (2010) published five-year results from the MAIN-COMPARE registry, evaluating PCA with stenting (n=1102) vs. surgical revascularization (n=1138) in patients with unprotected LMCA disease between 2000 and 2006. Of 1102 PCI patients, 318 received BMS and 784 received DES. Median follow-up was 5.2 years. After adjustment for differences in baseline risk factors, the five-year risk of death, Q wave MI, or stroke were not significantly different for patients treated with stenting vs. CABG. The risk of target vessel revascularization was significantly higher in the stented group than in the CABG group (p<0.001). Similar results were seen when

comparing BMS to CABG, and DES to CABG. The authors noted that a large randomized comparison study with CABG will provide more confidence in the long-term safety, durability and efficacy of PCI with DES for patients with unprotected LMCA disease.

Lee et al. (2010) published a meta-analysis of studies comparing CABG to PCI with DES in patients with unprotected LMCA narrowing. Two of the eight studies that met the inclusion criteria were randomized controlled trials; the other six were observational studies with matched cohorts or consecutive patients. Of 2905 patients, 1669 underwent CABG and 1236 underwent PCI with DES. The risk for death at one year did not differ significantly between the CABG and DES groups, nor did the risk for the composite of death, MI, or stroke. The risk for target vessel revascularization was significantly lower in the CABG group compared to the DES group.

A multicenter study by Boudriot et al. (2011) randomized patients with unprotected left main stem stenosis to SES (n=100) or CABG (n=101) to determine the effectiveness of DES vs. surgery. The combined rates for death and myocardial infarction at twelve months were comparable (surgery, 7.9%, SES, 5%), but stenting was inferior to surgery for rate of repeat revascularization (SES, 5.9% vs. CABG, 14%). Perioperative complications, including two strokes, were higher with surgery. The authors noted that a longer follow-up is warranted.

Pandya et al. (2011) conducted a meta-analysis to assess outcomes of DES and BMS in percutaneous coronary intervention (PCI) for unprotected left main coronary artery (LMCA) stenosis. A total of 44 studies (10,342 patients) met the inclusion criteria. The primary co-end points were mortality, MI, target vessel/lesion revascularization (TVR/TLR), and major adverse cardiac events (MACE): mortality, MI, and TVR/TLR. Crude event rates at three years for DES vs. BMS were: mortality: 8.8% vs. 12.7%; MI 4.0% vs. 3.4%; TVR/TLR, 8.0% vs. 16.4%; and MACE, 21.4% vs. 31.6%, respectively. The authors concluded that the results suggest that DES are associated with favorable outcomes compared to BMS for unprotected LMCA PCI, and support a continued re-evaluation of the role of PCI for treatment of unprotected LMCA disease. The authors acknowledged the limitations of this meta-analysis, however, including the use of a meta-analytical approach based on observational data. The results, particularly the use of crude event rates, were noted to be prone to confounding and selection bias; thus direct comparison of these overall rates was not performed.

There is insufficient evidence in the published medical literature to demonstrate the safety, efficacy and long-term outcomes of the use of DES in the treatment of unprotected LMCA disease. Well-designed randomized trials comparing the use of DES with bypass surgery are needed to establish the feasibility of DES for this expanded indication.

**Saphenous Vein Graft (SVG) Disease:** There are very few published studies evaluating the use of DES in the treatment of SVG lesions. Ge et al. (2005) published a retrospective study comparing clinical and angiographic outcomes of 61 consecutive patients who received DES with 89 patients who received BMS. The in-hospital MACE was similar in both groups, and the MACE rate at six months was 11.5% in the DES group and 28.1% in the BMS group. The DES group had a significantly lower rate of in-stent restenosis (10% vs. 26.7%). Not all patients received angiographic follow-up, however, and clinical follow-up was limited to seven months. The authors stated that the results are encouraging, but that the long-term clinical benefit of DES implantation in saphenous vein graft lesions remains to be determined, especially since 30–50% of late cardiac events in patients with saphenous vein graft lesions are due to disease progression at different sites.

Brilakis et al. (2009) conducted a randomized controlled trial to compare the frequency of angiographic restenosis and clinical events between a paclitaxel-eluting stent (PES) and similar bare metal stent (BMS) in SVG lesions. Patients were randomized to a BMS (39 patients, 43 grafts, 55 lesions) or to a PES (41 patients, 45 grafts, 57 lesions). Binary angiographic restenosis occurred in 51% of the lesions treated with BMS vs. 9% of the lesions treated with PES ( $p<0.0001$ ). At a median of 1.5 years follow-up, the PES patients had fewer target lesion revascularizations (28% vs. 5%,  $p=0.0003$ ) and target vessel failures (46% vs. 22%,  $p=0.03$ ). Mortality rates were similar in both groups. The authors noted that large, prospective, multicenter trials that use a clinical rather than angiographic end point are needed to confirm the beneficial role of DES in SVG lesions.

Brodie et al. (2009) evaluated outcomes of DES vs. BMS in saphenous vein grafts included in the multicenter U.S. STENT (Strategic Transcatheter Evaluation of New Therapies) registry. The study population included patients undergoing PCI of SVG lesions with DES (n=785) or BMS (n=343) who completed nine-month or two-year follow-up. The DES patients had fewer emergent procedures but had smaller vessels and longer lesions. The DES group had lower rates of death or MI at nine months ( $p=0.006$ ), and lower rates of death at two years

( $p=0.041$ ). Target vessel revascularization (TVR) was less with DES at nine months ( $p<0.001$ ) but was no different by two years ( $p=0.86$ ). DES reduced TVR rates at nine months in SVG lesions with diameter  $< 3.5$  mm ( $p=0.013$ ) but not in lesions  $\geq 3.5$  mm ( $p=0.74$ ).

Joyal et al. (2010) conducted a meta-analysis of the effectiveness and safety of DES in vein grafts. The analysis included 2 randomized controlled trials and 18 observational studies. In observational studies, DES were associated with a reduction in MACE, TVR, and TLR. The incidence of MI was similar between groups. Pooled results of the randomized controlled trials were inconclusive due to small sample size. The authors stated that data from observational studies should be interpreted with caution, and that there remains a need for large multicenter randomized controlled trials to address the effectiveness and safety of DES for graft stenosis.

There is insufficient evidence in the published medical literature to demonstrate the safety, efficacy and long-term outcomes of the use of DES in the treatment of SVG disease.

### **Thrombosis Following Drug-Eluting Stent Implantation**

Stent thrombosis after the implantation of BMS during PCI has long been recognized as a severe complication because of the high associated mortality. With the introduction of dual antiplatelet therapy consisting of clopidogrel and aspirin, the incidence of stent thrombosis decreased substantially. Most thromboses in BMS occurred within ten days of implantation, and thrombosis beyond 30 days of the procedure was rare. Patients in early DES clinical trials were prescribed aspirin indefinitely and clopidogrel for a minimum of two to three months in SES trials and six months in the PES trials. A number of published studies reported an increased risk of late stent thrombosis in patients treated with DES (Smith, et al., 2006; Luscher et al., 2007, Grines, et al., 2007).

BASKET-LATE (BAseL Stent Kosten Effektivitats Trial-Late Thrombotic Events), conducted by Pfisterer et al. for the BASKET-LATE investigators, was an observational study to define the incidence, timing and outcome of late clinical events and late stent thrombosis following discontinuation of clopidogrel in patients treated with DES vs. BMS. The authors stated that there is a growing concern that delayed endothelialization after DES implantation may lead to late stent thrombosis and related MI or death. The patient population consisted of patients who had been enrolled in the previously published BASKET trial. All 746 patients with 1133 stented lesions who survived six months without nonfatal MI or repeat target vessel revascularization were enrolled in the BASKET-LATE trial. Patients were followed for one year after discontinuation of clopidogrel. Rates of 18-month cardiac death or MI did not differ between the DES and BMS patients. After discontinuation of clopidogrel, between months seven and 18, these events occurred in 4.9% after DES vs. 1.3% after BMS implantation. Target vessel revascularization remained lower after DES, resulting in similar rates of all clinical events for this time period; 9.3% for DES vs. 7.9% for BMS. Late stent thrombosis and related death/target vessel MI were more frequent after DES vs. BMS implantation (2.6% vs. 1.3%, respectively). Thrombosis-related events occurred between 15 and 362 days after the discontinuation of clopidogrel and presented as MI or death in 88% of cases. The authors concluded that after the discontinuation of clopidogrel, the benefit of DES in reducing target vessel revascularization is maintained but has to be balanced against an increase in late cardiac death or nonfatal MI, possibly related to late stent thrombosis.

On January 4, 2007, the FDA published an updated statement drug-eluting stents, based on the recommendations of the Circulatory System Devices Panel panel. According to the statement, DES are associated with a small increase in stent thrombosis compared to BMS that emerges one year post-stent implantation, but based on the data available, this increased risk of stent thrombosis was not associated with an increased risk of death or MI. The concerns about thrombosis do not outweigh the benefits of DES compared to BMS when DES are implanted within the limits of their approved indications for use. The panel also addressed the broader use of DES in more complex patients than those studied to support initial marketing approval, stating that there off-label use of DES is associated with an increased risk of stent thrombosis, death or MI compared to on-label use. The FDA statement stressed the importance of adhering to recommendations for dual antiplatelet therapy.

In February 2007, the American Heart Association (AHA), American College of Cardiology (ACC), Society for Cardiovascular Angiography and interventions (SCAI), American College of Surgeons (ACS), and the American Dental Association (ADA), with representation from the American College of Physicians, issued a science advisory on the prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents. The advisory stressed the importance of adhering to ACC/AHA/SCAI percutaneous coronary intervention guideline recommendations for antiplatelet therapy. Current ACC/AHA/SCAI recommendations for

the prevention of stent thrombosis after coronary stent implantation state that, at a minimum, patients should be treated with clopidogrel 75 mg and aspirin 325 mg for one month after bare metal stent implantation, three months after sirolimus-eluting stent (SES) implantation, six months after paclitaxel-eluting stent (PES) implantation, and ideally, up to 12 months if they are not at high risk for bleeding. These recommendations were based on the antiplatelet regimen used in trials conducted to obtain FDA approval and on the anticipated time it takes for the stent struts to become adequately endothelialized to reduce the risk of stent thrombosis.

### **Cochrane Review**

A Cochrane systematic review was conducted by Greenhalgh et al. (2010) to assess the impact of DES versus BMS in the reduction of cardiac events. Evidence from randomized controlled trials comparing DES with BMS used in conjunction with percutaneous transluminal coronary angioplasty (PTCA) for treatment of angina or acute coronary syndrome were included in the review (n= >14,5000, 47 trials). The authors concluded that DES releasing sirolimus, paclitaxel, dexamethasone and zotarolimus reduce composite cardiac events, due largely to reductions in repeat revascularization rates. There was no evidence of a significant effect on rates of death, myocardial infarction (MI) or thrombosis.

### **ECRI**

An ECRI Institute evidence report, Drug-Eluting Stents for the Treatment of Coronary Artery Disease: Review of Systematic Reviews (ECRI, 2009), includes the following conclusions, and notes that the generalizability of these conclusions is confined to labeled DES uses in the general population.

- Use of sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) leads to a significantly lower revascularization incidence than bare metal stents (BMS). This benefit has been confirmed by randomized controlled trials (RCTs) and meta-analyses based on RCTs with follow-up as long as five years.
- While DES (SES or PES) may potentially lead to an increased risk of late or very late stent thrombosis, the cumulative MI and death rates for the reported follow-up periods (up to five years) are similar between DES and BMS.
- The RCT-based evidence favors SES over PES. While their safety profiles are similar, SES appear to lead to a significantly lower target lesion revascularization incidence than PES at the 6 to 12 or ≤30 month follow-ups. Future RCTs with large sample sizes and longer follow-up are needed to further compare the two stents.
- Early evidence suggests that everolimus-eluting stents (EES) and zotarolimus-eluting stents (ZES) lead to a significantly lower target lesion revascularization rate than BMS without causing additional harm. Future RCTs with larger sample sizes and longer follow-ups are needed to confirm these findings.
- Early evidence also suggests that EES and ZES may be as effective and safe as SES or PES for the treatment of coronary artery disease. Future RCTs with larger sample sizes and longer follow-ups are needed to further compare these DES.

**National Institute for Clinical Excellence (NICE) (United Kingdom):** NICE guidance on the use of coronary artery stents issued in October 2003 states that stents should be used routinely where PCI is the clinically appropriate procedure for patients with either stable or unstable angina or with acute MI. It is recommended that, when considering the use of a BMS or DES, the decision should be based on the anatomy of the target vessel for stenting and the symptoms and mode of presentation of the disease. The use of either a CYPHER or TAXUS stent is recommended in PCI for patients with symptomatic CAD in whom the internal diameter of the target artery is less than 3 mm or the lesion is longer than 15 mm. The guidance for the use of DES does not apply to patients who have had an MI in the preceding 24 hours or in whom there is angiographic evidence of thrombus in the target artery.

### **Professional Societies/Organizations**

In 2007, a focused update to the American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) 2005 guideline update for PCI was

published. This update included revisions to recommendations for the use of drug-eluting stents. The guideline classifies recommendations for treatments and procedures as follows:

Class I: Recommendation that procedure or treatment is useful/effective

- Level of evidence A: Sufficient evidence from multiple randomized trials or meta-analyses
- Level of evidence B: Limited evidence from single randomized trial or nonrandomized studies
- Level of evidence C: Only expert opinion, case studies, or standard of care

Class IIa: Recommendation in favor of treatment or procedure being useful/effective

- Level of evidence A: Some conflicting evidence from multiple randomized trials or meta-analyses
- Level of evidence B: Some conflicting evidence from single randomized trial or nonrandomized studies
- Level of evidence C: Only diverging expert opinion, case studies, or standard of care

Class IIb: Recommendation's usefulness/efficacy less well-established

- Level of evidence A: Greater conflicting evidence from multiple randomized trials or meta-analyses
- Level of evidence B: Greater conflicting evidence from single randomized trial or nonrandomized studies
- Level of evidence C: Only diverging expert opinion, case studies, or standard of care

Class III: Recommendation that procedure or treatment is not useful/effective and may be harmful

- Level of evidence A: Sufficient evidence from multiple randomized trials or meta-analyses
- Level of evidence B: Limited evidence from single randomized trial or nonrandomized studies
- Level of evidence C: Only diverging expert opinion, case studies, or standard of care

The ACC/AHA/SCAI 2007 update provides the following recommendations for the use of DES and BMS:

- **Class I, level of evidence A**

A DES should be considered as an alternative to a BMS in those patients for whom clinical trials indicate a favorable effectiveness/safety profile.

- **Class I, level of evidence B**

Before implanting a DES, the interventional cardiologist should discuss with the patient the need for and duration of dual antiplatelet therapy and confirm the patient's ability to comply with the recommended therapy for DES.

- **Class I, Level of evidence C**

In patients who are undergoing preparation for PCI and are likely to require invasive or surgical procedures for which dual antiplatelet therapy must be interrupted during the next 12 months, consideration should be given to implantation of a BMS or performance of balloon angioplasty with a provisional stent implantation instead of the routine use of a DES.

- **Class IIa, Level of evidence C**

In patients for whom the physician is concerned about risk of bleeding, a lower dose of 75 mg to 162 mg of aspirin is reasonable.

- **Class IIb, Level of evidence C**

A DES may be considered for clinical and anatomic settings in which the effectiveness/safety profile appears favorable but has not been fully confirmed by clinical trials.

The guideline states that outcomes up to four years for patients in the initial FDA-approval trials provide reassurance that, at least for those types of patients, there appears to be no increase in death or MI when comparing DES-treated groups with BMS-treated groups, despite a small excess of stent thrombosis. There are less data regarding outcomes for patients who receive a DES for "off-label" indications. These patients with coronary disease characteristics such as lesions in arteries less than 2.5 mm in diameter, very long lesions, bifurcation lesions, or a clinical syndrome such as acute MI, were excluded in the FDA-approval trials. Reports from large observational studies indicate that higher rates of repeat revascularization, death, and MI at one year are seen in these off-label patients. A similar relationship is seen in patients treated with BMS. There also

appears to be a significant association between off-label DES use and stent thrombosis. The selection of dual antiplatelet therapy may be different, therefore, when DES are used for off-label indications.

Focused updates of the ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction and the ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Kushner, et al., 2009) include the following revised recommendations for the use of drug-eluting stents:

**Class IIa, Level of evidence B:**

It is reasonable to use a DES as an alternative to a BMS for primary PCI in STEMI.

**Class IIb, Level of evidence B:**

A DES may be considered for clinical and anatomic settings in which the effectiveness/safety profile appears favorable but has not been fully confirmed by clinical trials. (Note: this recommendation was included in the 2007 PCI guideline described above, but with level of evidence C.)

The 2009 focused update states that there appears to be no difference between BMS and DES in mortality or MI rates and no difference in stent thrombosis risk. The major advantage of DES is a small reduction in target vessel revascularization rates. The greatest challenge in selecting patients for DES is in determining, in an emergency situation, whether the patient is a candidate for prolonged thienopyridine therapy. DES should be avoided in the presence of financial barriers to continuing prolonged dual-antiplatelet therapy, social barriers that could limit patient compliance or medical issues that involve bleeding risk or the need for invasive or surgical procedures in the subsequent year that would interrupt dual antiplatelet therapy.

**Summary**

Implantation of drug-eluting stents (DES) during percutaneous coronary intervention (PCI) has been shown to be an effective method of significantly reducing restenosis rates in selected patients when compared to PCI with bare-metal stents (BMS). Although early randomized trials had strict patient selection criteria, the use of DES has been broadly adopted for many indications beyond those evaluated in pivotal randomized controlled trials and approved by the U.S. Food and Drug Administration (FDA). There is adequate evidence that DES may be safe and effective for more complex coronary artery disease (e.g. small vessels, long lesions, multi-vessel disease) and in patients with ST-elevation myocardial infarction). There is insufficient evidence in the published medical literature, however, to demonstrate the safety and efficacy of DES for patients with unprotected left main coronary artery disease or saphenous vein graft disease.

Premature discontinuation of dual antiplatelet therapy has been identified as a significant contributing factor in thrombosis following DES implantation. Alternative treatment options should therefore be considered in patients who cannot comply with dual antiplatelet therapy for the prescribed period of time.

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**Coding/Billing Information**

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

| <b>CPT®*</b><br><b>Codes</b> | <b>Description</b>   |
|------------------------------|--|
| 92980                        | Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method, single vessel          |
| 92981                        | Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method, each additional vessel |

| <b>HCPCS</b><br><b>Codes</b> | <b>Description</b>  |
|------------------------------|---|
| G0290                        | Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method, single vessel |
| G0291                        | Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous,   |

with or without other therapeutic intervention, any method, each additional vessel

| ICD-9-CM Diagnosis Codes | Description  |
|--------------------------|--|
| 410.00-410-.92           | Acute myocardial infarction  |
| 411.0-411.89             | Other acute and subacute forms of ischemic heart disease   |
| 413.0-413.9              | Angina pectoris  |
| 414.01                   | Coronary atherosclerosis of native coronary artery   |
| 414.2                    | Chronic total occlusion of coronary artery   |
| 414.8                    | Other specific forms of chronic ischemic heart disease   |
| 414.9                    | Chronic ischemic heart disease, unspecified  |
| 447.1                    | Stricture of artery  |
| 996.74                   | Other complications due to other vascular device, implant, and graft (e.g., in-stent restenosis) |
|                          | Multiple/varied  |

#### Experimental/Investigational/Unproven/Not Covered:

| ICD-9-CM Diagnosis Codes | Description   |
|--------------------------|---|
| 414.02                   | Coronary atherosclerosis of autologous vein bypass graft  |
| 414.03                   | Coronary atherosclerosis of artery bypass graft; internal mammary artery                                  |
| 996.72                   | Other complications due to other cardiac device, implant, and graft (e.g., saphenous vein graft stenosis) |

\*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.

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## References

1. Applegate RJ, Sacrinty MT, Kutcher MA, Santos RM, Gandhi SK, Baki TT, Little WC. Off-label" stent therapy 2-year comparison of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2008 Feb 12;51(6):607-14.
2. Ardissino D, Cavallini C, Bramucci E, Indolfi C, Marzocchi A, Manari A, et al. Sirolimus-eluting vs. uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. JAMA. 2004 Dec 8;292(22):2727-34.
3. Bavry AA, Kumbhani DJ, Helton TJ, Bhatt DL. What is the risk of stent thrombosis associated with the use of paclitaxel-eluting stents for percutaneous coronary intervention?: a meta-analysis. J Am Coll Cardiol. 2005 Mar 15;45(6):941-6. m
4. Biondi-Zoccai GGI, Lotrionte M, Moretti C, Meliga E, Agostoni P, Valgimigli M, et al. A collaborative systematic review and meta-analysis on 1278 patients undergoing percutaneous drug-eluting stenting for unprotected left main coronary artery disease. Am Heart J. 2008 Feb;155(2):274-83. Epub 2007 Nov 26.
5. Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. Am Coll Cardiol. 2011 Feb 1;57(5):538-45.
6. Brilakis ES, Lichtenwalter C, de Lemos JA, Roesle M, Obel O, Haagen D, Saeed B, et al. A randomized controlled trial of a paclitaxel-eluting stent versus a similar bare-metal stent in

saphenous vein graft lesions the SOS (Stenting of Saphenous Vein Grafts) trial. *J Am Coll Cardiol*. 2009 Mar 17;53(11):919-28.

7. Brodie BR, Wilson H, Stuckey T, Nussbaum M, Laurent S, Bradshaw B, et al. Outcomes with drug-eluting versus bare-metal stents in saphenous vein graft intervention results from the STENT (strategic transcatheter evaluation of new therapies) group. *JACC Cardiovasc Interv*. 2009 Nov;2(11):1105-12.
8. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. *Circulation*. 2007 Mar 20;115(11):1440-55; discussion 1455. Epub 2007 Mar 7.
9. Chieffo A, Stankovic G, Bonizzoni E, Tsagalou E, Iakovou I, Montorfano M, et al. Early and mid-term results of drug-eluting stent implantation in unprotected left main. *Circulation*. 2005 Feb 15;111(6):791-5. Epub 2005 Feb 7.
10. Cosgrave J, Corbett SJ, Melzi G, Babic R, Biondi-Zoccai GGL, Airoidi F, et al. Late restenosis following sirolimus-eluting stent implantation. *Am J Cardiol*. 2007 Jul 1;100(1):41-4. Epub 2007 May 11.
11. Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, et al. on behalf of the TAXUS VI Investigators. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation*. 2005 Nov 22;112(21):3306-13. Epub 2005 Nov 14.
12. De Luca G, Stone GW, Suryapranata H, Laarman GJ, Menichelli M, Kaiser C, et al. Efficacy and safety of drug-eluting stents in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *Int J Cardiol*. 2009 Apr 3;133(2):213-22. Epub 2008 Apr 3
13. Dibra A, Kaastrati A, Alfonso F, Seyfarth M, Perez-Vizcayno Mj, et al. Effectiveness of drug-eluting stents in patients with bare-metal in-stent restenosis: meta-analysis of randomized trials. *J Am Coll Cardiol*. 2007 Feb 6;49(5):616-23. Epub 2006 Dec 4.
14. Di Lorenzo E, Sauro R, Varricchio A, Capasso M, Lanzillo T, Manganeli F, et al. Benefits of drug-eluting stents as compared to bare metal stent in ST-segment elevation myocardial infarction: four year results of the PaclitAxel or Sirolimus-Eluting stent vs bare metal stent in primary angioplasty (PASEO) randomized trial. *Am Heart J*. 2009 Oct;158(4):e43-50.
15. Douglas PS, Brennan JM, Anstrom KJ, Sedrakyan A, Eisenstein EL, Haque G, et al. Clinical effectiveness of coronary stents in elderly persons: results from 262,700 Medicare patients in the American College of Cardiology-National Cardiovascular Data Registry. *J Am Coll Cardiol*. 2009 May 5;53(18):1629-41
16. ECRI Institute. Drug-Eluting Stents for the Treatment of Coronary Artery Disease: Review of Systematic Reviews (early online final draft publication, uncopyedited).. Plymouth Meeting (PA): ECRI Institute Health Technology Assessment Information Service: 2009 Jan. 136 p. Available at URL address: <http://www.ecri.org>
17. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007 Jan 10;297(2):159-68. Epub 2006 Dec 5.
18. Ellis SG, Colombo , Grube E, Popma J, Koglin J, Dawkins KD, Stone GW. Incidence, timing, and correlates of stent thrombosis with the polymeric paclitaxel drug-eluting stent: a TAXUS II, IV, V, and VI meta-analysis of 3,445 patients followed for up to 3 years. *J Am Coll Cardiol*. 2007 Mar 13;49(10):1043-51. Epub 2007 Feb 26.

19. Epstein AJ, Polsky D, Yang F, Yang L, Groeneveld PW. Coronary revascularization trends in the United States, 2001-2008. *JAMA*. 2011 May 4;305(17):1769-76.
20. Fajadet J, Wiens W, Laarman GJ, Kuck KH, Ormiston J, Munzel T, for the ENDEAVOR II Investigators. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions. Clinical and angiographic results of the ENDEAVOR II Trial. *Circulation*. 2006 Aug 22;114(8):798-806. Epub 2006 Aug 14.
21. Galloe AM, Thuesen L, Kelbaek H, Thayssen P, Rasmussen, D, Hansen PR, for the SORT OUT II Investigators. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA*. 2008 Jan 30;299(4):409-16.
22. Ge L, Iakovou I, Sangiorgi GM, Chieffo A, Melzi G, Cosgrave J, Montorfano M, et al. Treatment of saphenous vein graft lesions with drug-eluting stents: immediate and midterm outcome. *J Am Coll Cardiol*. 2005 Apr 5;45(7):989-94.
23. Gershlick A, Kandzari DE, Leon MB, Wiens W, Meredith IT, Jajadet J, for the ENDEAVOR Investigators. Zotarolimus-eluting stents in patients with native coronary artery disease: clinical and angiographic outcomes in 1,317 patients. *Am J Cardiol*. 2007 Oct 22;100(8B):45M-55M.
24. Goy JJ, Stauffer JC, Siegenthaler M, Benoit A, Seydoux C. A prospective randomized comparison between paclitaxel and sirolimus stents in the real world of interventional cardiology: the TAXi trial. *J Am Coll Cardiol*. 2005 Jan 18;45(2):308-11.
25. Greenhalgh J, Hockenhull J, Rao N, Dundar Y, Dickson RC, Bagust A. Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. *Cochrane Database Syst Rev*. 2010 May 12;(5):CD004587
26. Grines CL, Bonow RO, Casey DE, Gardner TJ, Lockhart PB, Moliterno DJ, et al. American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, American Dental Association, American College of Physicians. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *Circulation*. 2007 Feb 13;115(6):813-8. Epub 2007 Jan 15.
27. Gurm HS, Boyden T, Welch KB. Comparative safety and efficacy of a sirolimus-eluting versus paclitaxel-eluting stent: a meta-analysis. *Am Heart J*. 2008 Apr;155(4):630-9. Epub 2008 Feb 21.
28. Hannan EL, Racz M, Holmes DR, Sharma S, Katz S, Walford, et al. comparison of mortality, myocardial infarction, and repeated revascularization for sirolimus-eluting and paclitaxel-eluting coronary stents. *Am Heart J*. 2007 Sep;154(3):545-53.
29. Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, et al. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med*. 2008 Jan 24;358(4):331-41.
30. Hodgson JM, Stone GW, Lincoff AM, Klein L, Walpole H, Bottner R, et al. Society for Cardiovascular Angiography and Interventions. Late stent thrombosis: considerations and practical advice for the use of drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force. *Catheter Cardiovasc Interv*. 2007 Feb 15;69(3):327-33.
31. Holmes DR, Kereiakes DJ, Laskey WK, Colombo A, Ellis, Henry, TD, et al. Thrombosis and drug-eluting stents: an objective appraisal. *J Am Coll Cardiol*. 2007 Jul 10;50(2):109-18. Epub 2007 May 22.

32. Holmes DR, Teirstein P, Satler L, Sketch M, O'Malley J, Popma JJ, et al. for the SISR Investigators. Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA*. 2006 Mar 15;295(11):1264-73. Epub 2006 Mar 12.
33. Jaffe R, Strauss BH. Late and very late thrombosis of drug-eluting stents: evolving concepts and perspectives. *J Am Coll Cardiol*. 2007 Jul 10;50(2):119-27. Epub 2007 May 22.
34. Jensen Lo, Maeng M, Kaltoft A, Thayssen P, Hansen HHT, Bottcher M, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol*. 2007 Jul 31;50(5):463-70. Epub 2007 Jun 29.
35. Joyal D, Filion KB, Eisenberg MJ. Effectiveness and safety of drug-eluting stents in vein grafts: a meta-analysis. *Am Heart J*. 2010 Feb;159(2):159-169.e4.
36. Kaiser C, Galatius S, Erne P, Eberli F, Alber H, Rickli H, et al.: BASKET-PROVE Study Group. Drug-eluting versus bare-metal stents in large coronary arteries. *N Engl J Med*. 2010 Dec 9;363(24):2310-9. Epub 2010 Nov 16.
37. Kandzari DE, Leon MB, Popma JJ, Fitzgerald PJ, O'Shaughnessy C, Ball MW for the ENDEAVOR III Investigators. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol*. 2006 Dec 19;48(12):2440-7. Epub 2006 Nov 28.
38. Kastrati A, Dibra A, Eberle S, Mehilli J, de Lezo JS, Goy JJ, et al. Sirolimus-eluting stents vs paclitaxel-eluting stents in patients with coronary artery disease: meta-analysis of randomized trials. *JAMA*. 2005 Aug 17;294(7):819-25.
39. Kastrati A, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J*. 2007 Nov;28(22):2706-13. Epub 2007 Sep 27.
40. Kastrati A, Mehilli J, von Beckerath N, Dibra A, Hausleiter J, Pache J, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs. balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA*. 2005 Jan 12;293(2):165-71.
41. King SB, Smith SC, Hirshfeld JW, Jacobs, Morrison DA, Williams DO. 2007 focused update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: (2007 Writing Group to Review New Evidence and Update the 2005 ACC/AHA/SCAI Guideline Update for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2008 Jan 15;172-209.
42. Kirtane AJ, Ellis SG, Dawlins KD, Colombo A, Grube E, Popma JJ, et al. Paclitaxel-eluting coronary stents in patients with diabetes mellitus: pooled analysis from 5 randomized trials. *J Am Coll Cardiol*. 2008 Feb 19;51(7):708-15.
43. Kirtane AJ, Gupta A, Iyengar S, Moses JW, Leon MB, Applegate R, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation*. 2009 Jun 30;119(25):3198-206. Epub 2009 Jun 15,
44. Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2009 Dec 1;54(23):2205-41
45. Laarman GJ, Suttorp MJ, Dirksen MT, van Heerebeek L, Kiemeneij F, Slagboom T, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med*. 2006 Sep 14;355(11):1105-13.

46. Kim HK, Jeong MH, Ahn YK, Kim JH, Chae SC, Kim YJ, , et al. Korea Acute Myocardial Infarction Registry Investigators. Comparison of outcomes between Zotarolimus- and sirolimus-eluting stents in patients with ST-segment elevation acute myocardial infarction. *Am J Cardiol.* 2010 Mar 15;105(6):813-8
47. Lee MS, Yang T, Dhoot J, Liao H. Meta-analysis of clinical studies comparing coronary artery bypass grafting with percutaneous coronary intervention and drug-eluting stents in patients with unprotected left main coronary artery narrowings. *Am J Cardiol.* 2010 Apr 15;105(8):1070-5. Epub 2010 Feb 20.
48. Lemos PA, Saia F, Hofma SH, Daemen J, Ong ATL, Arampatzis CA, et al. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol.* 2004;43(4):704-708.
49. Leon MB, Nikolsky E, Cutlip DE, Mauri L, Liberman H, Wilson H, et al.; ENDEAVOR IV Investigators. Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with de novo coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. *JACC Cardiovasc Interv.* 2010 Oct;3(10):1043-50.
50. Luscher TF, Steffel J, Eberli F, Joner M, Nakazawa G, Tanner FC, Virmani R. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation.* 2007 Feb 27;115(8):1051-8.
51. Mauri L, Hsieh W, Massaro JM, Kalon KLH, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med.* 2007 Mar 8;356(10):1020-9. Epub 2007 Feb 12.
52. Mehta RH, Leon MB, Sketch MH. The relation between clinical features, angiographic findings, and the target lesion revascularization rate in patients receiving the endeavor zotarolimus-eluting stent for treatment of native coronary artery disease: an analysis of ENDEAVOR I, ENDEAVOR II, ENDEAVOR II Continued Access Registry, and ENDEAVOR III. *Am J Cardiol.* 2007 Oct 22;100(8B):62M-70M.
53. Meier B, Sousa E, Guagliumi G, Van den Branden F, Grenadier E, Windecker S, et al. Sirolimus-eluting coronary stents in small vessels. *Am Heart J.* 2006 May;151(5):1026.e1-7.
54. Menichelli M, Parma A, Pucci E, Fiorilli R, de Felice F, Nazzaro M, Giulivi A, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol.* 2007 May 15;49(19):1924-30. Epub 2007 Apr 30.
55. Meredith IT, Ormiston J, Whitbourn R, Kay P, Muller D, Bonan R, et al., for the ENDEAVOR I Investigators. Four-year clinical follow-up after implantation of the endeavor zotarolimus-eluting stent: ENDEAVOR I, the first-in-human study. *Am J Cardiol.* 2007 Oct 22;100(8B):56M-61M.
56. Moreno R, Fernandez C, Hernandez R, Alfonso F, Angiolillo DJ, Sabate M, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol.* 2005 Mar 15;45(6):954-9.
57. Morice MC, Colombo A, Meier B, Serruys P, Tamburino C, Guagliumi G, et al. for the REALITY Trial Investigators. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. *JAMA.* 2006 Feb 22;295(8):895-904.
58. Morice JC, Serruys PW, Barragan P, Bode C, Van Es GA, Stoll HP, et al. Long-term clinical outcomes with sirolimus-eluting coronary stents: five-year results of the RAVEL trial. *J Am Coll Cardiol.* 2007 Oct 2;50(14):1299-304. Epub 2007 Sep 17.

59. Morice M, Serruys PW, Sousa JE, Fajadet J, Havashi EB, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346(23):1773-1780.
60. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, 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(14):1315-1323.
61. National Institute for Clinical Excellence (NICE). Guidance on the use of coronary artery stents. Technology appraisal 71. London, UK; NICE; 2003 Oct. Accessed May 3, 2011. Available at URL address: [www.nice.org.uk/](http://www.nice.org.uk/)
62. Ormiston A, Serruys PW, Regar E, Dudek D, Thuesen L, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet*. 2008 Mar 15;371(9616):899-907.
63. Pandya SB, Kim YH, Meyers SN, Davidson CJ, Flaherty JD, Park DW, et al. Drug-eluting versus bare-metal stents in unprotected left main coronary artery stenosis a meta-analysis. *JACC Cardiovasc Interv*. 2010 Jun;3(6):602-11.
64. Park DW, Seung KB, Kim YH, Lee JY, Kim WJ, Kang SJ, Lee SW, et al. Long-Term Safety and Efficacy of Stenting Versus Coronary Artery Bypass Grafting for Unprotected Left Main Coronary Artery Disease 5-Year Results From the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) Registry. *J Am Coll Cardiol*. 2010 Apr 30. [Epub ahead of print]
65. Park KW, Kang SH, Chung WY, Lee HY, Park JS, Kang HJ, et al. Real World' Comparison of Drug-Eluting Stents vs Bare Metal Stents in the Treatment of Unselected Patients With Acute ST-Segment Elevation Myocardial Infarction. *Circ J*. 2010 Apr 20. [Epub ahead of print]
66. Park SJ, Kim YH, Lee BK, Lee SW, Lee CW, Hong MK, Kim JJ, et al. Sirolimus-eluting stent implantation for unprotected left main coronary artery stenosis: comparison with bare metal stent implantation. *J Am Coll Cardiol*. 2005 Feb 1;45(3):351-6.
67. Pasceri V, Patti G, Speciale G, Pristipino C, Richichi G, Di Sciascio G, et al. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am Heart J*. 2007 May;153(5):749-54.
68. Pfisterer M, Brunner-La Rocca HP, Buser PT, Rickenbacher P, Hunziker P, for the BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol*. 2006 Dec 19;48(12):2584-91. Epub 2006 Nov 2.
69. Sakurai R, Hongo Y, Yamasaki M, Honda Y, Bonneau HN, Yock PG, et al., for the ENDEAVOR II Investigators. Detailed intravascular ultrasound analysis of Zotarolimus-eluting phosphorylcholine-coated cobalt-chromium alloy stent in de novo coronary lesions (results from the ENDEAVOR II trial). *Am J Cardiol*. 2007 Sep 1;100(5):818-23. Epub 2007 Jun 14.
70. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, Breithardt G, for the E-SIRIUS Investigators. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet*. 2003;362(9390):1093-1099.
71. Schomig A, Dibra A, Windecker S, Mehilli J, de Lizo JS, Kaiser C, et al. meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol*. 2007 Oct 2;50(14):1373-80. Epub 2007 Aug 21.

72. Serruys PW, Daemen J. Are drug-eluting stents associated with a higher rate of late thrombosis than bare metal stents? Late stent thrombosis: a nuisance in both bare metal and drug-eluting stents. *Circulation*. 2007 Mar 20;115(11):1433-9; discussion 1439. Epub 2007 Mar 7.
73. Serruys PW, Ong ATL, Morice MC, De Bruyne B, Colombo A, Macaya C, et al., on behalf of the ARTS II Investigators. Arterial revascularization therapies study part II-sirolimus-eluting stents for the treatment of patients with multivessel de novo coronary artery lesions. *EuroIntervention*. 2005;1:147-156.
74. Serruys PW, Onuma Y, Garg S, Vranckx P, De Bruyne B, Morice MC, et al.: ARTS II Investigators. 5-year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients with multivessel de novo coronary artery lesions. *J Am Coll Cardiol*. 2010 Mar 16;55(11):1093-101. Epub 2010 Feb 18.
75. Serruys PW, Silber S, Garg S, van Geuns RJ, Richardt G, Buszman PE, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med*. 2010 Jul 8;363(2):136-46. Epub 2010 Jun 16.
76. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007 Mar 8;356(10):989-97. Epub 2007 Feb 12.
77. Spaulding C, Teiger E, Commeau P, Varenne O, Bramucci E, Slama M, et al. Four-year follow-up of TYPHOON (trial to assess the use of the CYPHer sirolimus-eluting coronary stent in acute myocardial infarction treated with Balloon angioplasty). *JACC Cardiovasc Interv*. 2011 Jan;4(1):14-23.
78. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, et al. for the TAXUS V Investigators. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA*. 2005 Sep 14;294(10):1215-23.
79. Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350(3):221-231.
80. Stone GW, Ellis SG, O'Shaughnessy CD, Martine SI, Satler L, McGarry T, et al. for the TAXUS ISR Investigators. Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA*. 2006 Mar 15;295(11):1253-63. Epub 2006 Mar 12.
81. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, for the SPIRIT III Investigators. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA*. 2008 Apr 23;299(16):1903-13.
82. Stone GW, Midei M, Newman W, Sanz M, Hermiller JB, Williams J, for the SPIRIT III Investigators. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with denovo Native Coronary Artery Lesions (SPIRIT) III trial. *Circulation*. 2009 Feb 10;119(5):680-6. Epub 2009 Jan 26.
83. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007 Mar 8;356(10):998-1008. Epub 2007 Feb 12.
84. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Kolh P, Wijns W, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, et al. Guidelines on myocardial revascularization. *Eur J Cardiothorac Surg*. 2010 Sep;38 Suppl:S1-S52

85. Tsuchida K, Colombo A, Lefevre T, Oldroyd KG, Guetta V, Guagliumi G, et al. The clinical outcome of percutaneous treatment of bifurcation lesions in multivessel coronary artery disease with the sirolimus-eluting stent: insights from the Arterial Revascularization Therapies Study part II (ARTS II). *Eur Heart J*. 2007 Feb;28(4):433-42. Epub 2007 Jan 31.
86. U.S. Food and Drug Administration. Summary from the circulatory system devices panel meeting- Dec 7 & 8, 2006. Dec 15, 2006. Accessed May 3, 2011. Available at URL address: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfAdvisory/details.cfm?mtg=672>
87. van der Hoeven BL, Liem SS, Jukema JW, Suraphakdee N, Putter H, Dijkstra J, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. *J Am Coll Cardiol*. 2008 Feb 12;51(6):618-26.
88. Vink MA, Dirksen MT, Suttrop MJ, Tijssen JG, van Etten J, Patterson MS, et al. 5-year follow-up after primary percutaneous coronary intervention with a paclitaxel-eluting stent versus a bare-metal stent in acute ST-segment elevation myocardial infarction: a follow-up study of the PASSION (Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial. *JACC Cardiovasc Interv*. 2011 Jan;4(1):24-9.
89. Violini R, Musto C, De Felice F, Nazzaro MS, Cifarelli A, Petitti T, Fiorilli R. Maintenance of long-term clinical benefit with sirolimus-eluting stents in patients with ST-segment elevation myocardial infarction 3-year results of the SESAMI (sirolimus-eluting stent versus bare-metal stent in acute myocardial infarction) trial. *J Am Coll Cardiol*. 2010 Feb 23;55(8):810-4.
90. Windecker S, Remondino A, Eberli FR, Juni P, Raber L, Wenaweser P, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med*. 2005 Aug 18;353(7):653-62. Epub 2005 Aug 16.

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## Policy History

| <b>Pre-Merger Organizations</b> | <b>Last Review Date</b> | <b>Policy Number</b> | <b>Title</b>                                   |
|---------------------------------|-------------------------|----------------------|--|
| CIGNA HealthCare                | 6/15/2007               | 0092                 | Drug-Eluting Stents for Ischemic Heart Disease |

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