I. Aetna considers Food and Drug Administration (FDA)-approved everolimus-eluting stents (e.g., the Promus Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System, the Synergy Everolimus-Eluting Platinum Chromium Coronary Stent System and the Xience Alpine, Prime, Xpedition, and V Stent Systems), paclitaxel-eluting stents, sirolimus-eluting stents (e.g., the Taxus Express Paclitaxel-Eluting Coronary Stent System), zotarolimus-eluting stents (e.g., the Endeavor Zotarolimus-Eluting Coronary Stent System, the Resolute Integrity Zotarolimus-Eluting Coronary Stent, and the Resolute Onyx Zotarolimus-Eluting Coronary Stent System), and ridaforolimus-eluting stents (e.g., the EluNIR Ridaforolimus Eluting Coronary Stent System) medically necessary for members with angina pectoris (stable ischemic heart disease) or silent ischemia who are able to tolerate anti-platelet or anti-coagulant therapy, and who have any of the following:

- Coronary artery stenosis greater than or equal to 50 % in left main coronary artery; or
- Angina pectoris that is refractory, contraindicated, or intolerant to optimal medical therapy, and has greater than or equal to 70% stenosis in 1 or more coronary arteries; or
- Angina pectoris that is refractory, contraindicated or intolerant to optimal medical therapy and has coronary artery stenosis greater than 50% with fractional flow reserve (FFR) less than or equal to 0.80.

II. Aetna considers FDA-approved drug-eluting stents medically necessary for the treatment of intra-coronary stent re-stenosis.
III. Aetna considers drug-eluting stents experimental and investigational for treatment of all other indications, including any of the following (not an all-inclusive list) because their effectiveness for these indications has not been established:

- Aorto-arteritis (also known as Takayasu arteritis); or
- Chronic kidney disease with multi-vessel disease; or
- Esophageal stricture, dysphagia (benign or malignant); or
- Gastric outlet obstruction; or
- Pancreato-biliary diseases such as bile duct obstruction (including their use in endoscopic retrograde cholangiopancreatography); or
- Stenotic lesions of non-coronary arteries (e.g., carotid artery stenosis, intra-cranial atherosclerotic disease, peripheral vascular disease, renal artery stenosis, vertebral artery stenosis); or
- Vein graft stenosis; or
- Venous stenosis associated with dialysis vascular access

IV. Aetna considers biodegradable (bioresorbable, bioabsorbable, and magnetically-coated bioabsorbable) polymer drug eluting stents experimental and investigational because their effectiveness has not been established.

V. Aetna considers antibody coated coronary stents experimental and investigational because their safety and effectiveness has not been established.

Note: The use of intravascular optical coherence tomography (coronary native vessel or graft) or catheter-based coronary vessel or graft spectroscopy (e.g., infrared) during diagnostic evaluation and/or therapeutic intervention is considered integral to the primary procedure and not separately reimbursable.

'Aetna considers the Zilver PTX Drug-Eluting Peripheral Stent medically necessary for the primary treatment of femoropopliteal artery disease. See also CPB 0785 - Peripheral Vascular Stents (../700_799/0785.html).

See also CPB 0276 - Angioplasty and Stenting of Extra-Cranial and Intra-Cranial Arteries (../200_299/0276.html).

See also CPB 0625 - Dysphagia Therapy (0625.html).

Background
Drug-eluting coronary stents (DES) are placed during a percutaneous transluminal coronary angioplasty (PTCA), a procedure to dilate (widen) narrowed arteries of the heart. A catheter with a deflated balloon at its tip is inserted into a blood vessel in the arm or groin and advanced to the narrowed part of the coronary artery. The balloon is then inflated, pressing against the plaque and/or fatty materials and enlarging the inner diameter of the blood vessel so blood can flow more easily. The balloon is deflated and the catheter removed.

If a stent is to be placed, a stent delivery catheter is then threaded up into the affected area and a stent is left in place. Coronary stents are expandable metal mesh tubes that push against the walls of a coronary artery to keep it open. Due to problems with restenosis following the placement of these stents, drug-eluting stents were designed.

Drug-eluting stents are covered with a drug (e.g., everolimus, sirolimus, zotarolimus, paclitaxel, or ridaforolimus) that is slowly released to help prevent build-up of new tissue that grows in the artery, thereby preventing stenosis. Examples of US Food and Drug Administration (FDA) approved drug-eluting coronary stents may be found on the FDA website.

The use of stents has improved the results of percutaneous coronary re-vascularization. However, in-stent restenosis can occur due to neointimal proliferation of connective tissue. Prior to utilization of coronary stents, restenosis ranged between 32 to 55% of all angioplasties. With the placement of bare metal stents (BMS), the rate of restenosis dropped to 17 to 41%. The advent of DES, especially 2nd generation, and drug-coated balloon further reduced restenosis rates to less than 10% (Buccheri et al, 2016).

The macrolide anti-fungal agent sirolimus (rapamycin) has been shown to inhibit the proliferation of lymphocytes and smooth muscle cells and has been applied to the interior of balloon-expandable stents. The Rx Velocity consists of a stent coated with a mixture of synthetic polymers blended with sirolimus. The Rx Velocity is designed to release 80% of the drug within 30 days after stent implantation. Only a small amount of the drug is required, and systemic side effects from the drug are avoided.

The FDA approved the stent based on a review of 2 clinical studies of safety and effectiveness of the sirolimus-eluting stent. In a multi-center, randomized, double-blind, controlled clinical trial conducted in the United States (the SIRIUS study), 1,058 patients were randomly assigned to receive either the sirolimus-eluting stent or an uncoated stainless steel stent. Patients in the SIRIUS study had blockages of 15 mm to 30 mm long in arteries that were 2.5 mm to 3.5 mm wide.

Results were similar for both types of stents in the weeks immediately following the procedure, but after 9 months the patients who received the drug-eluting stent had a significantly lower rate of repeat procedures than patients who received the uncoated stent.

In addition, patients treated with the drug-eluting stent had a re-stenosis rate of 8.9 %, compared to 36.3 % of patients with the uncoated stent. The combined occurrence of repeat angioplasty, bypass surgery, myocardial infarction and death was 8.8 % for drug-eluting stent patients and 21 % for the uncoated stent patients. The types of adverse events seen with the drug-eluting stent were similar to those that occurred with the uncoated stent.

The FDA's approval of the sirolimus-eluting stent was also based on the results of a non-U.S. multi-center, randomized, double-blind, controlled clinical trial (the RAVEL study) comparing sirolimus-eluting stents with standard uncoated stents in 238 adults with stable or unstable angina pectoris or silent ischemia and single coronary lesions amenable to stenting. Lesions had to be between 2.5 mm and 3.5 mm in diameter, such that they could be covered by an 18 mm stent. Patients with complex coronary lesions, such as those containing substantial calcium or thrombus, were excluded from the study.

The investigators reported that use of a sirolimus-eluting stent resulted in the virtual elimination of angiographic evidence of neointimal hyperplasia and re-stenosis and greatly reduced the need for repeated re-vascularization procedures. At 6 months after stent placement, there was significantly less in-stent late luminal loss (a measure of neointimal proliferation) in patients receiving sirolimus-eluting stents than in patients receiving standard, uncoated stents. None of the patients receiving sirolimus-eluting stents had restenosis of 50 % or more of the luminal diameter, compared to 26.6 % of patients receiving standard stents. Within 1 year following stent placement, percutaneous re-vascularization had been performed in 22.9 % of recipients of standard, uncoated stents, and in none of the recipients of sirolimus-eluting stents. The investigators concluded that angina patients who received sirolimus-eluting stents had no angiographic evidence of late luminal loss or in-stent restenosis at 6 months after sirolimus-eluting stent placement and a very low rate of cardiovascular events within the year following stenting.

The safety and effectiveness of the Cypher stent in smaller diameter arteries or for longer blockage that required more than 2 stents was not studied in either trial. Also, the safety and effectiveness have not been studied in patients who are having a heart attack, patients who had previous intravascular radiation treatment, or patients who had their blockage in a bypass graft.

The FDA-approved labeling of the sirolimus-eluting stent warns that patients who are allergic to sirolimus or to stainless steel should not receive a Cypher stent. Caution is also recommended for people who have had recent cardiac surgery and for women who may be pregnant or who are nursing.
The FDA required the manufacturer of the sirolimus-eluting stent to conduct a 2,000-patient post-approval study and evaluate patients from ongoing clinical trials to assess the long-term safety and effectiveness to look for rare adverse events that may result from the use of this product.

The FDA approved the paclitaxel-eluting stents (Taxus Express Paclitaxel-Eluting Coronary Stent System, Boston Scientific Corporation) for improving luminal diameter for the treatment of de novo lesions less than 28 mm in length in native coronary arteries greater than or equal to 2.5 to less than or equal to 3.75 mm in diameter. Paclitaxel (Taxol) is similar to sirolimus in that it has been shown to inhibit proliferation of connective tissues and smooth muscle.

Stone et al (2004) reported on the results of the Taxus-IV trial, a multi-center prospective, randomized, double-blind controlled clinical trial of a paclitaxel-eluting stent in 1,314 patients with angina or provable ischemia who were receiving a stent in a single, previously untreated lesion in a native coronary artery. Patients in the Taxus-IV trial had vessel diameters between 2.5 and 3.75 mm, and had lesions between 10 to 28 mm in length that could be covered by a single stent. Patients with lesions of the left-main coronary artery were excluded. Patients were randomly assigned to receive either a bare-metal stent (BMS) or a paclitaxel-eluting stent (PES). At 9 months follow-up, the rate of target vessel re-vascularization due to ischemia was 12 % in patients who received the BMS, and 4.7 % in patients who received the PES (relative risk [RR] 0.39 (95 % confidence interval [CI]: 0.16 to 0.43). The rate of angiographic restenosis was 26.6 % in patients who received the BMS, and 7.9 % in patients who received the PES (RR 0.30 (95 % CI: 0.19 to 0.46). The rates of adverse events were similar between patients receiving the PES and the BMS.

The safety and effectiveness of the Taxus Express stent in smaller diameter arteries or for longer blockage that required more than 2 stents has not been studied. Also, the safety and effectiveness have not been studied in patients who are having a myocardial infarction, patients who had previous intravascular brachytherapy, or patients who had stenosis of a bypass graft.

The FDA-approved labeling of the PES warns that patients who are allergic to paclitaxel or to stainless steel should not receive a Taxus Express stent. Caution is also recommended for people who have had recent cardiac surgery and for women who may be pregnant or who are nursing.

The FDA required the manufacturer of the PES to conduct a 2,000 patient post-approval study and evaluate patients from ongoing clinical trials to assess the long-term safety and effectiveness to look for rare adverse events that may result from the use of this product.
The 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention states that most studies have defined a "significant" stenosis as 70% diameter narrowing; therefore, revascularization decisions and recommendations have been defined as 70% diameter narrowing (50% for left main CAD). Physiological criteria, such as an assessment of fractional flow reserve (FFR), has been used in deciding when revascularization is indicated. Thus, for recommendations about re-vascularization, coronary stenosis with FFR 0.80 can also be considered to be "significant".

Furthermore, the ACCF/AHA/SCAI 2011 guideline for percutaneous coronary intervention (PCI) provides the following recommendations for re-vascularization:

- Class I - CABG or PCI to improve symptoms is beneficial in patients with 1 or more significant (greater than or equal to 70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite guideline directed medical therapy (GDMT). (LOE: A)

- Left main CAD re-vascularization: Class IIa - PCI to improve survival is reasonable as an alternative to CABG in selected stable patients with significant (greater than 50% diameter stenosis) unprotected left main CAD who have:
  
  - Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (e.g., a low SYNTAX score [less than 22], ostial or trunk left main CAD); and
  
  - Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality greater than 5%). (LOE: B).

Per the 2014 European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines on myocardial re-vascularization, indications for re-vascularization in patients with symptomatic stable angina includes any coronary stenosis greater than 50% with an FFR less than or equal to 0.80, and is unresponsive to medical therapy (LOE: A).

The SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score may be helpful in formulating re-vascularization recommendations for persons with multiple complexities that may have a more favorable outcome with a CABG over a PCI. The ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS (2017) on appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease states that "although limitations of the SYNTAX score for certain re-vascularization recommendations are recognized and it may be impractical to apply this scoring system to all patients with multivessel disease, it is a reasonable surrogate for the extent and complexity of CAD and provides important information that can be helpful when making re-
vascularization decisions." A SYNTAX score of greater than 22 is associated with more favorable outcomes with CABG. A "significant" coronary stenosis can include 40 to 70 % luminal narrowing with an abnormal FFR, defined as less than or equal to 0.80. Although there are considerable data to support FFR-directed PCI treatment as an option, this concept is not well-established for surgical revascularization.

Per UpToDate on "Revascularization in patients with stable coronary artery disease: Coronary artery bypass graft surgery versus percutaneous coronary intervention", Cutlip and colleagues (2018) prefer PCI to CABG in most patients with single vessel non-left main CAD, defined as stenosis greater than or equal to 70 %, or 50 to 70 % with a fractional flow reserve (FFR) less than 0.80 in either the proximal or mid portion of the artery. The authors also state that although it is reasonable to use the SYNTAX score to help guide decision making on whether to recommend PCI versus CABG in patients with non-left main disease, no studies have shown that patients managed using this score have better outcomes than those who have not. The SYNTAX score II was better able to predict long-term mortality in patients with complex CAD than the angiographic SYNTAX score; however, while promising, further validation of this new score is needed.

Use of certain drug-eluting stents may be contraindicated in Individuals with known hypersensitivity to:

- Everolimus, paclitaxel, sirolimus, zotarolimus, ridaforolimus or structurally-related compounds (eg, polymethacrylates or polyolefin copolymers); or
- Materials used to make up the device or structurally-related compounds (eg, acrylic, cobalt, chromium, fluoropolymers, nickel, platinum, stainless steel, tungsten); or
- The polymer, its individual components or structurally-related compounds

Coronary artery stenting, regardless of stent type, is contraindicated for use in:

- Individuals who cannot receive recommended antiplatelet and/or anticoagulant therapy; or
- Individuals judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device.

In a randomized controlled trial (n = 57), Duda et al (2005) examined the safety and effectiveness of the sirolimus-eluting S.M.A.R.T. Nitinol Self-expanding Stent by comparison with a bare stent in superficial femoral artery (SFA) obstructions. These investigators concluded that although there is a trend for greater efficacy in the sirolimus-eluting stent group, there were no statistically significant differences in any of the variables.
Dzavik (2005) stated that bifurcation lesions have been recognized as one of the most important challenges facing interventional cardiologists since the start of PCI. The potential of peri-procedural occlusion of the side branch (SB) was found to be significant, resulting in early attempts at protecting the SB with a 2nd guide wire and kissing balloon inflation in order to minimize this risk, and thus improve the procedural and short-term success of the procedure. The advent of stenting significantly improved the safety of the procedure, although, SB success continued to be a challenge. A variety of single- as well as double-stenting techniques were developed that improved the safety and short-term results of PCI involving SB. Long-term success, however, continued to elude, as a consequence of an increased need for target lesion revascularization (TLR) and higher major adverse cardiac event (MACE) rates following PCI of bifurcation lesions. The introduction of drug-eluting stents appears to have brought bifurcation PCI to a new level of long-term efficacy. Specialty bifurcation stents have been developed to provide easy access to the SB, however, these have to date had little impact on practice and have not been adopted widely. New techniques such as crush stenting and its several permutations, and simultaneous kissing stenting developed specifically for drug-eluting stents have been developed. Debate continues as to which the most effective technique is. True randomized comparisons are, however, lacking. It is likely that all of the currently utilized techniques have a place in interventional cardiologists’ quiver, and that each is appropriate in a particular anatomical scenario. Nonetheless, well-designed randomized studies assessing the various bifurcation techniques especially in complex bifurcation lesions are needed. Moreover, Iakovou et al (2005) reported that the cumulative incidence of stent thrombosis 9 months after successful drug-eluting stent implantation in consecutive “real-world” patients was substantially higher than the rate reported in clinical trials. Premature anti-platelet therapy discontinuation, renal failure, bifurcation lesions, diabetes, and low ejection fraction were identified as predictors of thrombotic events.

At the 2006 European Society/World Congress of Cardiology, results of 3 studies suggested that DES may lead to an increased risk of death and cardiac events compared with BMS. One study suggested an increase in death and Q-wave myocardial infarction (MI) in subjects receiving a sirolimus-eluting stent, while the other indicated that this type of DES might increase non-cardiac mortality.

In the first study, Camenzind and associates performed a meta-analysis on randomized clinical studies comparing 1st-generation DES with BMS. Sirolimus-eluting stent trials entailed the RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS, and included 878 patients fitted with the novel stent and 870 who received BMS. The PES trials entailed TAXUS II, IV, V, and VI, and included information on 1,685 patients fitted with this stent and 1,675 who received BMS. The pooled incidence of death and Q-wave MI combined, analyzed from within the program by time points of follow-up, was significantly higher with the sirolimus-eluting stent than the BMS at 3 years, at 6 % versus 4 %, representing a 33 % relative increase in risk. In PES trials, the incidence of the combined endpoint at 3 years was 3.5 % with the DES
compared with 3.1% for the BMS. Pooling the latest follow-up data from each trial program revealed that the incidence all-cause death or MI was 2.4% higher with the sirolimus-eluting stent than the BMS (6.3% versus 3.9%) and 0.3% higher for PES than the BMS (2.6% versus 2.3%). Further analysis indicated that the rate of total mortality and Q-wave MI combined was a significant 38% higher with the sirolimus-eluting stent versus the BMS (p = 0.03), while there was a trend towards a 16% higher incidence with the PES. These researchers warned against indiscriminate use of 1st-generation DES and said that use of BMS may still be maintained, while awaiting safer 2nd-generation DES.

In the second study, Nordmann et al conducted a meta-analysis of randomized controlled trials that compared sirolimus-eluting stents and PES with BMS in their effect on total, cardiac, and non-cardiac mortality using last follow-up data. They found that although there was a trend to benefits with the DES for reducing total mortality at 1 year compared with BMS, there was a trend to increased mortality in years 2, 3, and 4 of follow-up. Furthermore, at 2 and 3 years' follow-up, there was increased non-cardiac mortality (cancer, lung disease, and stroke) with the sirolimus-eluting stent versus the BMS (odds ratio = 2.74 and 2.04, respectively), the majority of which related to cancer. These investigators concluded that preliminary evidence suggests that sirolimus-eluting stents but not PES may lead to increased non-cardiac mortality. Follow-up and assessment of cause-specific deaths in patients receiving DES are mandatory to determine the safety of these devices.

A third study tracked stent thrombosis rates in 8,000-plus patients enrolled in studies in Holland and Switzerland. Wenaweser reported that over 3 years, the cumulative rate of thrombosis was 2.9%, but what was disturbing was that the rate was linear -- starting at 1.2% at 30 days (similar to BMS) and then 0.6% each year thereafter. Unlike BMS, thrombosis did not seem to wane with time, but continued to increase at the same rate, confirming concerns that DES suppress cell growth too much in some individuals, opening the door to thrombosis, which have serious consequences.

In the light of ongoing concerns over the safety of DES, the Society for Cardiovascular Angiography and Interventions (SCAI) issued guidelines for use of the devices (Hodgson et al, 2007). The guidelines advise physicians to ensure that patients meet published guidelines' criteria for percutaneous coronary intervention before implantation of any stent. The guidelines also recommend that the physician decide on an individual-patient basis whether a DES, BMS, or surgical revascularization is most appropriate; discuss the risks and benefits with the patient; and document it in the medical record. The guidelines recommended that providers know which patients (those with diabetes, renal failure, etc.) and lesions (complex, long, small-diameter, etc.) carry high-risk for thrombosis with DES. Ideally, physicians should assess patients' likelihood of long-term compliance with dual antiplatelet therapy before implantation. Continuation for 1 year is strongly recommended in patients not at high risk for bleeding, and continuation beyond 1 year should be considered in patients at higher risk for stent thrombosis.
Tu and colleagues (2007) stated that the placement of DES decreases the frequency of repeat re-vascularization procedures in patients undergoing PCI in randomized clinical trials. However, there is uncertainty about the effectiveness of DES, and increasing concern about their safety, in routine clinical practice. From the Cardiac Care Network of Ontario's population-based clinical registry of all patients undergoing PCI in Ontario, Canada, these investigators identified a well-balanced cohort of 3,751 pairs of patients, matched on the basis of propensity score, who received either BMS alone or DES alone during an index PCI procedure between December 1, 2003, and March 31, 2005. The primary outcomes of the study were the rates of target-vessel re-vascularization, MI, and death. The 2-year rate of target-vessel re-vascularization was significantly lower among patients who received DES than among those who received BMS (7.4 % versus 10.7 %, p < 0.001). Drug-eluting stents were associated with significant reductions in the rate of target-vessel re-vascularization among patients with 2 or 3 risk factors for re-stenosis (i.e., presence of diabetes, small vessels [less than 3 mm in diameter], and long lesions [greater than or equal to 20 mm]) but not among lower-risk patients. The 3-year mortality rate was significantly higher in the BMS group than in the DES group (7.8 % versus 5.5 %, p < 0.001), whereas the 2-year rate of MI was similar in the 2 groups (5.2 % and 5.7 %, respectively; p = 0.95). The authors concluded that DES are effective in reducing the need for target-vessel re-vascularization in patients at highest risk for re-stenosis, without a significantly increased rate of death or MI.

In a meta-analysis, Stettler et al (2007) compared the safety and effectiveness of 2 DES (sirolimus-eluting stent and PES) and BMS. These investigators searched relevant sources from inception to March, 2007, and contacted investigators and manufacturers to identify randomized controlled trials in patients with coronary artery disease that compared DES with BMS, or that compared sirolimus-eluting stents head-to-head with PES. Safety outcomes included mortality, MI, and definite stent thrombosis; the effectiveness outcome was target lesion re-vascularization. These researchers included 38 trials (18,023 patients) with a follow-up of up to 4 years. Trialists and manufacturers provided additional data on clinical outcomes for 29 trials. A network meta-analysis with a mixed-treatment comparison method to combine direct within-trial comparisons between stents with indirect evidence from other trials while maintaining randomization was performed. Mortality was similar in the 3 groups: hazard ratios (HR) were 1.00 (95 % CI: 0.82 to 1.25) for sirolimus-eluting versus BMS, 1.03 (0.84 to 1.22) for PES versus BMS, and 0.96 (0.83 to 1.24) for sirolimus-eluting versus PES. Sirolimus-eluting stents were associated with the lowest risk of MI (HR 0.81, 95 % CI: 0.66 to 0.97, p = 0.030 versus BMS; 0.83, 0.71 to 1.00, p = 0.045 versus PES). There were no significant differences in the risk of definite stent thrombosis (0 days to 4 years). However, the risk of late definite stent thrombosis (greater than 30 days) was increased with PES (HR 2.11, 95 % CI: 1.19 to 4.23, p = 0.017 versus BMS; 1.85, 1.02 to 3.85, p = 0.041 versus sirolimus-eluting stents). The reduction in target lesion re-vascularization seen with DES compared with BMS was more pronounced with sirolimus-eluting stents than
with PES (0.70, 0.56 to 0.84; p = 0.0021). The authors concluded that the risks of mortality associated with DES and BMS are similar. Sirolimus-eluting stents seem to be clinically better than BMS and PES.

In a meta-analysis, Schomig et al (2007) made a synthesis of the available evidence on the relative safety and effectiveness of 2 DES: (i) sirolimus-eluting stents (SES) and (ii) PES in patients with coronary artery disease. A total of 16 randomized trials of SES versus PES with a total number of 8,695 patients were included in this analysis. A full set of individual outcome data from 5,562 patients was also available. Mean follow-up period ranged from 9 to 37 months. The primary effectiveness end point was the need for re-intervention (target lesion re-vascularization). The primary safety end point was stent thrombosis. Secondary end points were death and recurrent MI. No significant heterogeneity was found across trials. Compared with PES, SES significantly reduced the risk of re-intervention (HR 0.74; 95% CI: 0.63 to 0.87, p < 0.001) and stent thrombosis (HR 0.66; 95% CI: 0.46 to 0.94, p = 0.02) without significantly impacting on the risk of death (HR 0.92; 95% CI: 0.74 to 1.13, p = 0.43) or MI (HR 0.84; 95% CI: 0.69 to 1.03, p = 0.10). The authors concluded that SES are superior to PES in terms of a significant reduction of the risk of re-intervention and stent thrombosis. The risk of death was not significantly different between the 2 DES, but there was a trend toward a higher risk of MI with PES, especially after the first year from the procedure. The observation that SES are superior to PES is in agreement with the analysis from Gurm et al (2008) who reported that patients treated with SES appear to have a significantly lower risk of re-stenosis and need for target vessel re-vascularization compared with those treated with PES.

The National Institute for Health and Clinical Excellence’s (NICE, 2008) recommended the use of DES for the treatment of coronary artery disease only if the target artery to be treated has less than a 3-mm caliber or the lesion is longer than 15 mm, and the price difference between DES and BMS is no more than 300 pounds sterling.

Pfisterer et al (2009) evaluated the long-term benefit-risk ratio of DES versus BMS relative to stent size. All 826 consecutive BASKET (BAse Stent Kosten-Effektivitäts Trial) patients randomized 2:1 to DES versus BMS were followed after 3 years. Data were analyzed separately for patients with small stents (less than 3.0 mm vessel/less than 4.0 mm bypass grafts, n = 268) versus only large stents (greater than or equal to 3.0 mm native vessels, n = 558). Clinical events were related to stent thrombosis. Three-year clinical target vessel revascularization (TVR) rates remained borderline reduced after DES [9.9 versus 13.9 % (BMS), p = 0.07], particularly in patients with small stents (10.7 versus 19.8 %, p = 0.03; large stents: 9.5 versus 11.5 %, p = 0.44). Cardiac death/MI rates (12.7 versus 10.0 %, p = 0.30) were similar, however, death/MI beyond 6 months was higher after DES [9.1 versus 3.8 % BMS, p = 0.009], mainly due to increased late death/MI in patients with large stents (9.7 versus 3.1 %, p = 0.006). The results paralleled findings for stent thrombosis. The authors concluded that the clinical benefit of DES was maintained at no overall increased
risk of death or death/MI up to 3 years. However, death/MI rates were increased in DES versus BMS patients beyond 6 months, especially in patients with large stents, paralleling findings for stent thrombosis. Thus, stent size appears to influence the 3-year benefit-risk ratio after DES implantation.

Kirtane and colleagues (2009) performed a meta-analysis of DES studies to estimate the relative impact of DES versus BMS on safety and efficacy end points, particularly for non-FDA-labeled indications. Comparative DES versus BMS studies published or presented through February 2008 with greater than or equal to 100 total patients and reporting mortality data with cumulative follow-up of greater than or equal to 1 year were identified. Data were abstracted from studies comparing DES with BMS; original source data were used when available. Data from 9,470 patients in 22 randomized controlled trials (RCTs) and from 182,901 patients in 34 observational studies were included. Observational and RCT data were analyzed separately. In RCTs, DES (compared with BMS) were associated with no detectable differences in overall mortality (HR, 0.97; 95 % CI: 0.81 to 1.15; p = 0.72) or MI (HR, 0.95; 95 % CI: 0.79 to 1.13; p = 0.54), with a significant 55 % reduction in target vessel re-vascularization (HR, 0.45; 95 % CI: 0.37 to 0.54; p < 0.0001); point estimates were slightly lower in off-label compared with on-label analyses. In observational studies, DES were associated with significant reductions in mortality (HR, 0.78; 95 % CI: 0.71 to 0.86), MI (HR, 0.87; 95 % CI: 0.78 to 0.97), and TVR (HR, 0.54; 95 % CI: 0.48 to 0.61) compared with BMS. The authors concluded that in RCTs, no significant differences were observed in the long-term rates of death or MI after DES or BMS use for either off-label or on-label indications. In real-world non-randomized observational studies with greater numbers of patients but the admitted potential for selection bias and residual confounding, DES use was associated with reduced death and MI. Both RCTs and observational studies demonstrated marked and comparable reductions in target vessel re-vascularization with DES compared with BMS. These data in aggregate suggested that DES are safe and efficacious in both on-label and off-label use, but highlighted differences between RCT and observational data comparing DES and BMS.

In a systematic review and meta-analysis, Brar et al (2009) compared outcomes by stent type for death, MI, TVR, and stent thrombosis in RCTs of ST-segment elevation myocardial infarction (STEMI). A secondary analysis was performed among registry studies. These investigators searched Medline, Embase, the Cochrane Library, and Internet sources for articles comparing outcomes between DES and BMS among patients with STEMI between January 2000 and October 2008. Randomized controlled trials and registries including patients 18 years of age and older receiving a DES or BMS were included. These researchers extracted variables related to the study design, setting, participants, and clinical end points. A total of 13 RCTs were identified (n = 7,352). Compared with BMS, DES significantly reduced TVR (relative risk [RR]: 0.44; 95 % CI: 0.35 to 0.55), without increasing death (RR: 0.89; 95 % CI: 0.70 to 1.14), MI (RR: 0.82; 95 % CI: 0.64 to 1.05), or stent thrombosis (RR: 0.97; 95 % CI: 0.73 to 1.28). These observations were durable over 2
years. Among 18 registries (n = 26,521), DES significantly reduced TVR (RR: 0.54; 95% CI: 0.40 to 0.74) without an increase in MI (RR: 0.87, 95% CI: 0.62 to 1.23). Death was significantly lower in the DES group within 1 year of the index PCI, but there were no differences within 2 years (p = 0.45). The authors concluded that the use of DES appears safe and efficacious in RCTs and registries of patients with STEMI. The DES significantly reduce TVR compared with BMS, without an increase in death, MI, or stent thrombosis within 2 years of the index procedure.

Trikalinos and associates (2009) noted that over the past 2 decades, percutaneous transluminal balloon coronary angioplasty (PTCA), BMS, and DES succeeded each other as catheter-based treatments for coronary artery disease. These researchers carried out a systematic overview of RCTs comparing these interventions with each other and with medical therapy in patients with non-acute coronary artery disease. They searched Medline for trials contrasting at least 2 of the 4 interventions (PTCA, BMS, DES, and medical therapy). Eligible outcomes were death, MI, coronary artery bypass grafting, TLR/TVR, and any re-vascularisation. Random effects meta-analyses summarized head-to-head (direct) comparisons, and network meta-analyses integrated direct and indirect evidence. A total of 61 eligible trials (25,388 patients) investigated 4 of 6 possible comparisons between the 4 interventions; no trials directly compared DES with medical therapy or PTCA. In all direct or indirect comparisons, succeeding advancements in PCI did not produce detectable improvements in deaths or MI. The RR for indirect comparisons between DES and medical therapy was 0.96 (95% CI: 0.60 to 1.52) for death and 1.15 (0.73 to 1.82) for MI. By contrast, these investigators recorded sequential significant reductions in target lesion or vessel re-vascularisation with BMS compared with PTCA (RR 0.68 [0.60 to 0.77]) and with DES compared with BMS (0.44 [0.35 to 0.56]). The RR for the indirect comparison between DES and PTCA for TLR/TVR was 0.30 (0.17 to 0.51). The authors concluded that sequential innovations in the catheter-based treatment of non-acute coronary artery disease showed no evidence of an effect on death or MI when compared with medical therapy. These results lend support to present recommendations to optimize medical therapy as an initial management strategy in patients with this disease.

Biondi-Zoccai et al (2008) conducted a systematic review of basic science and clinical evidence on the Xience V everolimus-eluting stents (EES), by thoroughly searching PubMed and online databases (updated September 2007). They also compared the clinical results of Xience V versus PES (Taxus) and SES (Cypher) by means of direct and indirect comparison meta-analysis. A total of 3 clinical studies has been retrieved focusing on Xience V, however both most recent and important trials were still unpublished. The first trial compared Xience V versus BMS, whereas the other 2 RCTs compared Xience V versus Taxus. Direct meta-analysis of Xience V versus Taxus showed that Xience V was significantly superior to Taxus in preventing binary angiographic re-stenosis and TVR (p < 0.05 for both). Indirect comparison between Xience V and Cypher, exploiting a recent 16-trial large meta-analysis, showed that Xience V was at least as effective as Cypher in

preventing TVR (p = 0.12). The authors concluded that EES (Xience V) appear as a major breakthrough in coronary interventions, and superior efficacy has already been demonstrated in comparison to PES (Taxus). Data available to date also suggested that Xience V is at least as effective as SES (Cypher). Whether long-term results and direct comparison to Cypher will also be favorable remains to be established by future clinical trials.

Stone and colleagues (2009) reported the 2-year clinical follow-up data of EES in the treatment of patients with de novo native coronary artery lesions (SPIRIT) III trial. A total of 1,002 patients with up to 2 de novo native coronary artery lesions (reference vessel diameter, 2.5 to 3.75 mm; lesion length less than or equal to 28 mm) were randomized 2:1 to EES versus PES. Anti-platelet therapy consisted of aspirin indefinitely and a thienopyridine for greater than or equal to 6 months. Between 1 and 2 years, patients treated with EES compared with PES tended to have fewer episodes of protocol-defined stent thrombosis (0.2 % versus 1.0 %; p = 0.10) and MI (0.5 % versus 1.7 %; p = 0.12), with similar rates of cardiac death (0.3 % versus 0.3 %; p = 1.0) and TVR (2.9 % versus 3.0 %; p = 1.0). As a result, at the completion of the 2-year follow-up, treatment with EES compared with PES resulted in a significant 32 % reduction in target vessel failure (10.7 % versus 15.4 %; HR, 0.68; 95 % CI: 0.48 to 0.98; p = 0.04) and a 45 % reduction in major adverse cardiac events (cardiac death, MI, or target lesion revascularization; 7.3 % versus 12.8 %; hazard ratio, 0.55; 95 % CI: 0.36 to 0.83; p = 0.004). Among the 360 patients who discontinued clopidogrel or ticlopidine after 6 months, stent thrombosis subsequently developed in 0.4 % of EES patients versus 2.6 % of PES patients (p = 0.10). The authors concluded that patients treated with EES rather than PES experienced significantly improved event-free survival at a 2-year follow-up in the SPIRIT III trial, with continued divergence of the hazard curves for target vessel failure and major adverse cardiac events between 1 and 2 years evident. The encouraging trends toward fewer stent thrombosis episodes after 6 months in EES-treated patients who discontinued a thienopyridine and after 1 year in all patients treated with EES rather than PES deserve further study.

Chevalier and associates (2008) compared zotarolimus-eluting stents (ZES) with PES in a randomized trial of percutaneous intervention for de novo coronary artery stenosis. The primary end point was defined as non-inferiority of in-segment late lumen loss after 9 months. A total of 29 investigative sites in Europe, Australia, as well as New Zealand enrolled 401 patients, 396 of whom received a study stent. After 9 months, late lumen loss was significantly greater in the ZoMaxx group (in-stent 0.67 +/- 0.57 mm versus 0.45 +/- 0.48 mm; p < 0.001; in-segment 0.43 +/- 0.60 mm versus 0.25 +/- 0.45 mm; p = 0.003), resulting in significantly higher rates of greater than 50 % angiographic re-stenosis (in-stent 12.9 % versus 5.7 %; p = 0.03; in-segment 16.5 % versus 6.9 %; p = 0.007). The upper bound of the 95 % CI on the difference in in-segment late lumen loss between the 2 treatment groups (0.27 mm) exceeded the 0.25 mm value pre-specified for non-inferiority. There were no significant differences between ZoMaxx and Taxus-treated groups with
respect to TVR (8.0 % versus 4.1 %; p = 0.14), major adverse cardiac events (12.6 % versus 9.6 %; p = 0.43), or stent thrombosis (0.5 % in both groups). The authors concluded that after 9 months, ZES showed less neointimal inhibition than PES, as shown by higher in-stent late loss and re-stenosis by qualitative coronary angiography.

Waseda and colleagues (2009) compared the vessel response between ZES and PES using intra-vascular ultrasound (IVUS). Data were obtained from patients with serial (baseline and 8-months follow-up) IVUS analysis available (n = 198). Volumetric analysis was performed for vessel, lumen, plaque, stent, and neointima. Cross-sectional narrowing (given as percentage) was defined as neointimal area divided by stent area. Neointima-free frame ratio was calculated as the number of frames without IVUS-detectable neointima divided by the total number of frames within the stent. Subsegment analysis was performed at every matched 1-mm subsegment throughout the stent. At follow-up, the ZES group showed significantly greater percentage of neointimal obstruction (16.6 +/- 12.0 % versus 9.9 +/- 8.9 %, p < 0.01) and maximum cross-sectional narrowing (31.8 +/- 16.1 % versus 25.2 +/- 14.9 %, p < 0.01) with smaller minimum lumen area than the PES group did. However, the incidence of maximum cross-sectional narrowing greater than 50 % was similar in the 2 groups. Neointima-free frame ratio was significantly lower in the ZES group. In overall analysis, whereas the PES group showed positive remodeling during follow-up (13.7 +/- 4.2 mm(3)/mm to 14.3 +/- 4.3 mm(3)/mm), the ZES group showed no significant difference (12.7 +/- 3.6 mm(3)/mm to 12.9 +/- 3.5 mm(3)/mm). In subsegment analysis, significant focal positive vessel remodeling was observed in 5 % of ZES and 25 % of PES cases (p < 0.05). The authors concluded that there were different global and focal vessel responses for ZES and PES. Both DES showed a similar incidence of lesions with severe narrowing despite ZES having a moderate increase in neointimal hyperplasia compared with neointimal hyperplasia in PES. There was a relatively lower neointima-free frame ratio in ZES, suggesting a greater extent of neointimal coverage.

The Endeavor ZES from Medtronic received FDA approval on February 1, 2008, while Xience V EES from Abbott Vascular was approved by FDA on July 2, 2008 (Doostzadeh et al, 2010).

Machan (2006) reviewed the use of DES outside the coronary artery. The majority of research and clinical data on DES are from their use in coronary artery atherosclerosis; however, these devices can be used outside the coronary circulation in both vascular and non-vascular structures. In non-coronary arteries the principal indication for DES is the same as in the coronary circulation, prevention of re-stenosis. Human experience has been essentially limited to trials or compassionate use; 2 small controlled studies and a number of small observational single-center reports have been published, and there are trials in progress. To date, the data have not been as compelling as in the coronary circulation. The physical characteristics of each vascular bed such as external compressive forces, blood flow rates, wall thickness relative to lumen size, as well as vessel wall composition differ
significantly from the coronary circulation and each presents unique challenges to local drug delivery. Outside the vascular bed, the principal expected use is the prevention of tissue ingrowth following stent insertion in tubular structures such as the trachea, esophagus or bile ducts. The authors concluded that considerable further study of DES is needed in each anatomical region to determine the ideal stent/drug combination and clinical appropriateness.

Nakagawa (2011) stated that the effectiveness of the use of DES in the treatment of STEMI, a representative condition of acute coronary syndrome, is still unknown. In this article, data of registry, randomized, and meta-analyses studies were reviewed. Drug eluting stents showed a consistent trend toward decreasing the risk of repeat re-vascularization without increasing the incidence of death, recurrent MI, and stent thrombosis as compared to BMS. The findings concerning the use of DES in patients with STEMI are:

(i) its short-term effect of reducing the re-stenosis and repeat re-vascularization rates is evident; (ii) no randomized studies have demonstrated the usefulness of DES in the prevention of death and recurrent MI; (iii) no randomized or meta-analyses studies have shown results sufficient to eliminate long-term safety concerns; and most importantly, and (iv) there are no data clearly indicating safety concerns.

Palmerini et al (2012) compared the risk of thrombosis between BMS and DES. For this network meta-analysis, RCTs comparing different DES, or DES with BMS currently approved in the United States were identified through Medline, Embase, Cochrane databases, and proceedings of international meetings. Information about study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted. A total of 49 trials including 50,844 patients randomly assigned to treatment groups were analysed. One-year definite stent thrombosis was significantly lower with cobalt-chromium everolimus eluting stents (CoCr-EES) than with BMS (odds ratio [OR] 0.23, 95 % CI: 0.13 to 0.41). The significant difference in stent thrombosis between CoCr-EES and BMS was evident as early as 30 days (OR 0.21, 95 % CI: 0.11 to 0.42) and was also significant between 31 days and 1 year (OR 0.27, 95 % CI: 0.08 to 0.74). CoCr-EES were also associated with significantly lower rates of 1-year definite stent thrombosis compared with paclitaxel-eluting stents (OR 0.28, 95 % CI: 0.16 to 0.48), permanent polymer-based sirolimus-eluting stents (OR 0.41, 95 % CI: 0.24 to 0.70), phosphorylcholine-based zotarolimus-eluting stents (OR 0.21, 95 % CI: 0.10 to 0.44), and Resolute zotarolimus-eluting stents (OR 0.14, 95 % CI: 0.03 to 0.47). At 2-year follow-up, CoCr-EES were still associated with significantly lower rates of definite stent thrombosis compared with BMS (OR 0.35, 95 % CI: 0.17 to 0.69) and paclitaxel-eluting stents (OR 0.34, 95 % CI: 0.19 to 0.62). No other DES had lower definite thrombosis rates compared with BMS at 2-year follow-up. The authors concluded that in RCTs completed to date, CoCr-EES has the lowest rate of...
stent thrombosis within 2 years of implantation. The finding that CoCr-EES also reduced stent thrombosis compared with BMS, if confirmed in future RCTs, represents a paradigm shift.

De Luca and colleagues (2012) performed a meta-analysis using individual patient data to evaluate the long-term safety and effectiveness of DES compared with BMS in patients undergoing primary PCI for STEMI. Formal searches of electronic databases (MEDLINE and CENTRAL) and scientific session presentations from January 2000 to June 2011 were carried out. These investigators examined all completed randomized trials of DES for STEMI. Individual patient data were obtained from 11 of 13 trials identified, including a total of 6,298 patients (3,980 [63.2 %] randomized to DES [99 % sirolimus-eluting or paclitaxel-eluting stents] and 2,318 [36.8 %] randomized to BMS). At long-term follow-up (mean [SD], 1,201 [440] days), DES implantation significantly reduced the occurrence of TVR (12.7 % versus 20.1 %; hazard ratio [95 % CI], 0.57 [0.50 to 0.66]; p < 0.001, p value for heterogeneity, 0.20), without any significant difference in terms of mortality, re-infarction, and stent thrombosis. However, DES implantation was associated with an increased risk of very late stent thrombosis and re-infarction. The authors concluded that the present pooled patient-level meta-analysis demonstrated that among patients with STEMI undergoing primary PCI, sirolimus-eluting and paclitaxel-eluting stents compared with BMS are associated with a significant reduction in TVR at long-term follow-up. Although there were no differences in cumulative mortality, re-infarction, or stent thrombosis, the incidence of very late re-infarction and stent thrombosis was increased with these DES.

On November 28, 2017, the FDA granted premarket approval for Medinol’s EluNIR Ridaforolimus Eluting Coronary Stent System for the treatment of narrowing or blockage of coronary arteries caused by CAD. This device is indicated for improving coronary luminal diameter in patients with symptomatic heart disease due to de novo lesions less than or equal to 30 mm in length in native coronary arteries with reference diameter of 2.50 mm to 4.25 mm. The EluNIR RES is designed with a novel metallic spring tip and narrow strut width to assist clinicians in highly complex anatomy and disease (Cardinal Health, 2017). The stent is permanently implanted within the coronary artery to help keep the artery open, while the drug, ridaforolimus, is released over time to help prevent the blood vessel from re-narrowing (FDA, 2017).

FDA (2018) labeling includes the following contraindications for the EluNIR RES:

- Patients who cannot receive recommended anti-platelet and/or anti-coagulant therapy
- Patients judged to have a lesion which prevents complete inflation of the angioplasty balloon or proper placement of the stent or delivery system
- Patients with hypersensitivity or allergies to aspirin, heparin, clopidogrel, ticlopidine, drugs such as ridaforolimus or similar drugs, the polymer or its individual
components CarboSil 20 55D and Poly n-Butyl Methacrylate, cobalt, chromium, nickel, molybdenum, or contrast media.

Kandzari et al (2017) conducted a prospective, international, multi-center, 1:1 randomized trial (BIONICS trial) to compare ridaforolimus- and zotarolimus-eluting coronary stents in patients with CAD. The aim was to evaluate in a non-inferiority design the relative safety and efficacy of ridaforolimus-eluting stents (RESs) and slow-release zotarolimus-eluting stents among 1,919 patients undergoing PCI. Inclusion criteria allowed for recent MI, total occlusions, bifurcations lesions, and other complex conditions. At 12 months, the primary end-point of target lesion failure (composite of cardiac death, target vessel-related MI, and TLR) was 5.4 % for both devices (p non-inferiority = 0.001). Definite/probable stent thrombosis rates were low in both groups (0.4 % RES versus 0.6 % zotarolimus-eluting stent, p = 0.75); 13-month angiographic in-stent late lumen loss was 0.22 ± 0.41 mm and 0.23 ± 0.39 mm (p non-inferiority = 0.004) for the RES and zotarolimus-eluting stent groups, respectively, and intravascular ultrasound percent neointimal hyperplasia was 8.10 ± 5.81 and 8.85 ± 7.77, respectively (p non-inferiority = 0.01). The authors concluded that their findings support the safety and efficacy of RESs, and that RESs met the pre-specified criteria for non-inferiority compared with zotarolimus-eluting stents for the primary end-point of target lesion failure at 12 months. (NCT01995487).

Paradies et al. (2018) conducted a prospective, multi-center, single-blind, randomized trial comparing the novel ridaforolimus-eluting BioNIR stent to the zotarolimus-eluting Resolute stent. Patients with stable CAD or acute coronary syndromes (ACS) were randomly assigned to treatment with BioNIR or the Resolute stent. The primary end-point was angiographic in-stent late lumen loss (LLL) at 6 months. A total of 302 patients were randomized, of whom 27.8 % were diabetic and 30.1 % presented with ACS; 86 % of patients underwent 6-month angiographic follow-up. The BioNIR stent was shown to be non-inferior to the Resolute stent for the primary end-point of in-stent LLL at 6 months (p < 0.0001). At 12-months follow-up, target lesion failure (TLF) occurred in 3.4 % in the ridaforolimus group and 5.9 % in the zotarolimus group (p = 0.22). Rates of MACE were similar between the BioNIR and Resolute Integrity groups (4.3 % versus 5.9 %, respectively, p = 0.45). The authors concluded that clinical outcomes at 1 year were comparable between the BioNIR and Resolute Integrity stents, and that the BioNIR stent was non-inferior to the Resolute for the primary end-point of angiographic in-stent LLL at 6 months.

Aorto-Arteritis (Takayasu Arteritis)

In a recent review on advances in the medical and surgical treatment of aorto-arteritis (also known as Takayasu arteritis), an inflammatory vascular disorder that produces arterial stenoses and aneurysms primarily involving the thoraco-abdominal aorta and its branches
and the pulmonary arteries, Liang and Hoffman (2005) stated that new drugs that target intimal hyperplasia, as well as drug-eluting stents, deserve to be studied for possible utility as adjuncts to present treatments.

Wang and colleagues (2015) investigated the long-term outcomes of DES implantation in patients with Takayasu arteritis (TAK). Data were summarized retrospectively on a cohort of 48 TAK patients with CAD who received DES implantation and hospitalization from February 2004 to March 2014. TAK patients exhibited increased mean ± SD brachial-ankle pulse wave velocity (baPWV) compared with patients with CAD (p = 0.002). However, CAD patients had higher levels of low-density lipoprotein cholesterol (p = 0.04). Multiple linear regression analysis revealed that baPWV was independently associated with the extent of CAD, assessed by the SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) score (β = 0.33, Pp= 0.03), in TAK patients. DES implantation was deployed in 73 coronary lesions in 48 TAK patients, and re-stenosis occurred in 48 lesions after an average of 25.6 months following intervention. Logistic regression analysis identified that a baPWV of 17.00 meters/second or higher (p = 0.008) may be considered as an independent predictor of DES restenosis. Moreover, the multi-variate Cox proportional hazards model demonstrated that a baPWV of 17.00 meters/second or higher (p = 0.003) was significant and may serve as an independent predictor of MACE in TAK patients who underwent DES implantation. The investigators concluded that DES in-stent restenosis (ISR) remains a challenge, affecting the long-term outcomes of patients with TAK. They suggested that measuring increased arterial stiffness through baPWV, with the addition of inflammation status monitoring during follow-up, would be of great clinical value to identify TAK patients with DES who have a high risk for ISR and MACE. Study was limited to relatively small sample size.

Chronic Kidney Disease with Multi-Vessel Disease

Wang and colleagues (2017b) noted that the optimal re-vascularization strategy of coronary artery bypass grafting (CABG) versus PCI with DES (PCI-DES) in patients with CKD and multi-vessel disease (MVD) remains unclear. In a meta-analysis, these researchers compared CABG and PCI-DES in these patients. PubMed, Embase and Cochrane Library electronic databases were searched from inception until June 2016. Studies that evaluated the comparative benefits of DES versus CABG in CKD patients with MVD were considered for inclusion. They pooled the ORs from individual studies and conducted heterogeneity, quality assessment and publication bias analyses. A total of 11 studies with 29,246 patients were included (17,928 DES patients; 11,318 CABG). Compared with CABG, pooled analysis of studies showed DES had higher long-term all-cause mortality (OR, 1.22; p < 0.00001), CD (OR, 1.29; p < 0.00001), MI (OR, 1.89; p = 0.02), repeat re-vascularization (OR, 3.47; p < 0.00001) and major adverse cardiac and cerebrovascular events (MACCE) (OR, 2.00; p = 0.002), but lower short-term all-cause mortality (OR, 0.33; p < 0.00001) and cerebro-vascular accident (CVA) (OR, 0.64; p = 0.0001). Subgroup analysis restricted to
patients with ESRD yielded similar results, but no significant differences were found regarding CVA and MACCE. The authors concluded that CABG for patients with CKD and MVD had advantages over PCI-DES in long-term all-cause mortality, MI, repeat re-vascularization and MACCE, but the substantial disadvantage in short-term mortality and CVA. They stated that future large RCTs are needed to confirm these findings.

Esophageal Stricture, Dysphagia (Benign or Malignant)

Kochar and Shah (2013) discussed the significant advances in endoscopic techniques and the development of high-quality stents. The authors reported that endoscopic enteral stent placement is increasingly being performed for the management of malignant GI obstruction. Palliative stenting is now routinely performed for malignant esophageal, gastric, duodenal, and colon obstruction. In addition to palliative indications, pre-operative stenting in the colon may be performed as a bridge to surgery to achieve immediate decompression and convert an emergent surgery into an elective, 1-stage procedure. The realm of enteral stenting has recently expanded to include management of benign conditions such as leaks, fistulas, and benign strictures in the GI tract. Further research is required to study the use of enteral stents in benign conditions and to adequately compare endoscopic stent placement with surgical intervention. The authors concluded that promising new technologies such as biodegradable stents and DES require further investigation. With continued innovation in endoscopic techniques and stenting devices, the field of enteral stenting is likely to expand further with an increase in indications and improvement in outcomes.

Wang et al (2014) discussed temporary placement of a paclitaxel or rapamycin-eluting stent to reduce stenting induced inflammatory reaction and scarring in benign cardia stricture dog models. A total of 80 dog models of stricture were randomly divided into a control group (CG, n = 20, no stent insertion), a bare stent group (BSG, n = 20), a paclitaxel eluting (PacI-ESG, n = 20) and a rapamycin eluting stent group (Rapa-ESG, n = 20), with 1-week stent retention. Lower-esophageal-sphincter pressure (LOSP), 5-minute barium height (5-mBH) and cardia diameter were assessed before, immediately after the procedure, and regularly for 6 months. Five dogs in each group were euthanized for histological examination at each follow-up assessment. Stent insertion was well-tolerated, with similar migration rates in 3 groups. At 6 months, LOSP and 5-mBH improved in PacI-ESG and Rapa-ESG compared to BSG (p < 0.05), with no difference between PacI-ESG and Rapa-ESG (p > 0.05). Cardia kept more patency in the PacI-ESG and Rapa-ESG than in BSG (p < 0.05). Reduced peak inflammatory reactions and scarring occurred in the PacI-ESG and Rapa-ESG compared to BSG (p < 0.05), with a similar outcome in the PacI-ESG and Rapa-ESG (p > 0.05). The authors concluded that paclitaxel or rapamycin-eluting stents insertion led to better outcomes than bare stents in benign cardia stricture dog models.
Zhang et al (2017) evaluated the efficiency and safety of paclitaxel-eluting SEMSs (PEMSs) in rabbit esophageal cancer models. The authors noted that use of self-expanding metallic stents (SEMSs) is the current treatment of choice for malignant gastro-intestinal obstructions. However, these stents can promote only drainage and have no antitumor effect. Some studies have reported that drug-eluting SEMSs may have tumor inhibition potential. A PEMS was covered with a paclitaxel-incorporated membrane, in which the concentration of paclitaxel was 10% (wt/vol). The rabbit models were created endoscopically. Then, a PEMS or SEMS was endoscopically inserted into the rabbit esophagus; 2 weeks after stent placement, the rabbits were sacrificed, and these researchers evaluated the tumor volume, area of the wall defect, area of the tumor under endoscopic ultrasound (EUS) before and after stent placement, status of the proximal esophageal obstruction, tumor metastasis food-intake and weight loss. A total of 26 rabbits received stent insertion and survived until sacrifice, and migration occurred in 4 cases, 3 in SEMS group and 1 in PEMS group. For the remaining 22 rabbits, at the sacrificed time, the average tumor volume was 7.00 ± 4.30 cm³ in the SEMS group and 0.94 ± 1.51 cm³ in the PEMS group (p < 0.05). The area of the esophageal wall defect was 0.70 ± 0.63 cm² in the SEMS group and 0.17 ± 0.16 cm² in the PEMS group (p < 0.05). The tumor area under EUS was 4.40 ± 1.47 cm² in the SEMS group and 1.30 ± 1.06 cm² in the PEMS group (p < 0.05). At the time of stent placement, tumor area under EUS was comparable in the 2 groups. Other indices did not significantly differ between the 2 groups. The authors concluded that SEMS and PEMS are both safe and effective to relieve dysphagia in rabbit esophageal cancer models. A PEMS can serve as an alternative tool for advanced esophageal cancer that may inhibit tumor growth by serving as a drug sustained-release platform. Clinical trials of the stent are warranted in the future.

UpToDate reviews on "Management of benign esophageal strictures" (Guelrud, 2017) and "Use of expandable stents in the esophagus" (Baron and Law, 2017) do not mention use of drug-eluting stents in the treatment of esophageal strictures (malignant or benign).

Gastric Outlet Obstruction

McLoughlin and Byrne (2008) stated that self-expanding metal stents (SEMS) play an important role in the management of patients with malignant obstructing lesions in the gastrointestinal tract. Traditionally, they have been used for palliation in malignant gastric outlet and colonic obstruction as well as esophageal malignancy. The development of the polyflex stent, which is a removable self-expanding plastic stent, allows temporary stent insertion for benign esophageal disease and possibly for patients undergoing neoadjuvant chemotherapy prior to esophagectomy. Potential complications of SEMS insertion include perforation, tumor overgrowth or ingrowth, and stent migration. Newer stents are being developed with the aim of increasing technical and clinical success rates, while reducing complication rates. Other areas of development include biodegradable stents for benign disease and radioactive or drug-eluting stents for malignant disease. It is hoped that, in the
future, newer stents will improve the management of these difficult conditions and, possibly, provide prognostic as well as symptomatic benefit in the setting of malignant obstruction.

Katsanos et al (2010) noted that minimally invasive image-guided insertion of SEMS in the upper gastrointestinal tract is the current treatment of choice for palliation of malignant esophageal or gastro-duodenal outlet obstructions. These investigators presented a concise review of contemporary stenting practice of the upper gastrointestinal tract, and the procedures in terms of appropriate patient evaluation, indications, and contra-indications for treatment were analyzed, along with available stent designs, procedural steps, clinical outcomes, inadvertent complications, and future technology. Latest developments include biodegradable polymeric stents for benign disease and radioactive or drug-eluting stents for malignant obstructions.

Pancreato-Biliary Diseases

Lee (2009) noted that in unresectable malignant bile duct obstruction, endoscopic stent insertion is the treatment of choice. However, the current stent allows only mechanical palliation of the obstruction, and has no anti-tumor effect. Currently, in the vascular field, the DES is very highly favored. The requirements for a DES in a non-vascular tract, such as the bile duct, are far different from those of a DES to be used in the vascular tract. The non-vascular DES must suppress tumor proliferation and mucosal hyperplasia. For example, the non-vascular stent might be covered with a membrane that gradually releases a chemotherapeutic agent. Currently, there is not much experience with DES in the bile duct. Nevertheless, these researchers are continuously testing many anti-tumor agents in animal and human studies. The authors concluded that they expect and hope DES will work effectively for tumor cells in diverse ways and, more importantly, will prolong stent patency and the patients' survival periods. However, considerable investigation and a clinical study of DES will be required to achieve these goals.

Jang and colleagues (2017) initiated a double-blind, prospective, randomized comparative study to evaluate the efficacy of a multiplex paclitaxel-eluting stent, using a Pluronic mixture membrane (MSCPM-II), versus a covered metal stent (CMS) in patients with malignant biliary obstruction. The prospective randomized trial was closed early because of a high incidence of early occlusion. Therefore, the data were analyzed using the intent-to-treat method. A total of 72 patients with unresectable distal malignant biliary obstructions were prospectively enrolled. The results showed that the 2 groups did not differ significantly in basic characteristics and mean follow-up period (MSCPM-II 194 days versus CMS 277 days, p = 0.063). Stent occlusion occurred in 14 patients (35 %) who received MSCP M-II and in 7 patients (21.9 %) who received CMSs. Stent patency and survival time did not significantly differ between the 2 groups (p = 0.355 and p = 0.570). The complications were
mild and resolved by conservative management in both groups. The authors concluded that there were no significant differences in stent patency or patient survival in MSCPM-II and CMS patients with malignant biliary obstructions.

Stenotic Lesions of Non-Coronary Arteries

Shammas and Dippel (2005) stated that peripheral vascular disease (PVD) is very prevalent in the United States. Patients with PVD have a heightened inflammatory state and are at high-risk of death from acute cardiovascular problems rather than from progression of PVD. Modifiable risk factors for PVD include smoking, hypertension, diabetes, hyperlipidemia, elevated high sensitivity C-reactive protein, obesity, and the metabolic syndrome.

Symptomatic treatment of claudication includes smoking cessation, exercise, cilostazol, statins, and re-vascularization with percutaneous or surgical therapy. Anti-thrombotic therapy with aspirin or clopidogrel is important to reduce cardiovascular events but does not affect symptoms of claudication. Patients with rest limb ischemia or ulceration should be re-vascularized to minimize the chance of limb loss. Percutaneous re-vascularization is not without significant complications, however, and future research needs to focus on inflammation, thrombosis, and restenosis in the PVD patient. Furthermore, new devices that tackle difficult lesions, drug-eluting stents, and pharmacological agents that reduce global atherosclerosis are on the horizon, and are likely to become critical components in the management of the PVD patient.

Owens et al (2011) stated that the endovascular management of symptomatic atherosclerotic SFA disease is challenging and requires consideration of unique anatomical, hemodynamic, and biomechanical factors. The current armamentarium of balloon catheters and flexible nitinol BMS have limited long-term effectiveness due to intimal hyperplasia resulting in re-stenosis. Unfortunately, the remarkably low re-stenosis rates achieved with drug-eluting stents (DES) placed in the coronary vasculature has not been replicated in the femoral artery. The reason for this is multi-factorial including delivery platforms, drug and dosage selection and trial design flaws. Currently, however, there are several novel therapies and delivery platforms in the development pipeline that have exhibited biologic effectiveness in pre-clinical and early clinical trials. While these offer promise in improving outcomes following lower extremity intervention, caution is warranted until the safety of these new technologies can be ensured.

Ott et al (2017) stated that “atherosclerosis in the SFA is common in patients suffering from peripheral artery disease. Paclitaxel-eluting balloon (PEB) angioplasty, stenting and directional atherectomy (DA) have provided new options for the treatment of SFA disease; however the comparative efficacy remains uncertain. A total of 155 patients with symptomatic peripheral artery disease with de novo SFA stenotic or occlusive lesions were randomized to treatment with plain balloon angioplasty (BA) followed by PEB angioplasty and stenting (n = 48), BA followed by stenting (n = 52) or directional DA with distal protection
and bailout stenting (n = 55). The primary end-point of the study was percentage diameter stenosis after 6 months measured by angiography. Other end-points included TLR, thrombosis, ipsilateral amputation, binary re-stenosis and all-cause mortality at 6 and 24 months. Baseline and lesion characteristics were comparable in all groups with a mean lesion length of 65.9 ± 46.8 mm and 56 % total occlusions. At 6 months angiography, the percent diameter stenosis was significantly lower in patients treated by PEB angioplasty followed by stent (34 ± 31 %) as compared with BA followed by stenting (56 ± 29 %, p = 0.009) or DA (55 ± 29 %, p = 0.007). Similarly, binary re-stenosis was significantly lower after treatment with PEB angioplasty as compared with BA or DA. Clinical follow-up at 24 months revealed improved TLR after PEB angioplasty followed by stenting as compared with BA followed by stenting or DA. No differences between the groups were found in target lesion thrombosis or mortality rates, and no patient underwent amputation. The authors concluded that treatment of de novo superficial femoral artery lesions with PEB angioplasty followed by stenting was superior to BA and stenting or DA regarding angiographic diameter stenosis at 6 months and TLR at 24 months.

Werner et al (2012) presented the 5-year angiographical and clinical results of a retrospective registry assessing the performance of sirolimus-eluting stents (SES) in the treatment of infra-popliteal atherosclerotic disease. From 2004 to 2009, a total of 158 patients (95 men; mean age of 71.9 years) with chronic lower limb ischemia (Rutherford categories 3 to 6) underwent primary SES placement in focal infra-popliteal lesions. The angiographical endpoint was patency, defined as freedom from in-stent stenosis (ISS) greater than 50 %. Clinical endpoints were death, amputation, and bypass surgery. Results were correlated with patient and lesion characteristics and cumulative outcomes were assessed with Kaplan-Meier analysis. Technical success was achieved in all cases. The primary patency rates were 97.0 % after 6 months, 87.0 % after 12 months, and 83.8 % at 60 months. In-stent stenosis was predominantly observed in the first year after stent placement. Female gender was associated with a higher rate of ISS. During clinical follow-up of 144 (91 %) patients over a mean 31.1 +/- 20.3 months, there were 27 (18.8 %) deaths, 4 (2.8 %) amputations, and no bypass surgery. Clinical status improved in 92 % of the patients with critical limb ischemia (CLI) and 77 % of the patients suffering from claudication (p = 0.022). The authors concluded that treatment of focal infra-popliteal lesions with SES showed encouraging long-term angiographical results in this registry. Clinical improvement was evident, but more pronounced in CLI patients than in patients suffering from claudication. They stated that further studies are needed to evaluate the potential clinical benefit of SES as compared to balloon angioplasty or BMS in the treatment of infra-popliteal lesions.

Bosiers et al (2017) investigated the efficacy of the paclitaxel-coated, self-expanding, nitinol Stentys Stent System in tibioperoneal arterial lesions less than or equal to 50 mm long. The prospective, single-arm, multi-center PES-BTK-70 trial (ClinicalTrials.gov identifier NCT01630070) evaluated the safety and efficacy of the coronary Stentys Stent System in
the treatment of a stenotic or occlusive lesion less than or equal to 50 mm long in the tibioperoneal arteries of patients with critical limb ischemia (CLI). Between January 2012 and May 2013, a total of 70 patients with CLI received a Stentys DES for the treatment of infrapopliteal stenosis or occlusion. The mean lesion length was 17.2 mm. The primary outcome measures were primary patency at 6 months (duplex ultrasound) and 12 months (angiography). Secondary outcomes included limb salvage and freedom from TLR. The investigators stated that technical and procedure success (less than 30 % residual stenosis without major complications) was achieved in 68 (97.1 %) of 70 cases. Primary patency was 87.6 % (95 % CI: 83.5 % to 91.7 %) at 6 months and 72.6 % (95 % CI: 66.9 % to 78.3 %) at 1 year. Freedom from TLR was 79.1 % at 1 year (95 % CI: 73.9 % to 84.3 %) and limb salvage was 98.5 % (95 % CI: 97.0 to 100.0). No stent fractures were found by core laboratory review of all follow-up imaging data available up to 12 months. The investigators concluded that the self-expanding, nitinol, paclitaxel-eluting, coronary Stentys stent was found to be safe and effective in the below-the-knee region, with results similar to the most recent limus-eluting stent trials.

Spreen et al (2017) conducted a multi-center, randomized comparison study (PADI trial) to evaluate the performance of paclitaxel-eluting DESs and percutaneous transluminal angioplasty with bare metal stent (PTA-BMS) in infrapopliteal lesions causing clinical limb ischemia (CLI). Adults with critical limb ischemia (Rutherford category greater than or equal to 4) and infrapopliteal lesions were randomized to receive PTA-BMS or DESs with paclitaxel. Long-term follow-up consisted of annual assessments up to 5 years after treatment or until a clinical end point was reached. Clinical end points were major amputation (above ankle level), infrapopliteal surgical or endovascular reintervention, and death. Preserved primary patency (less than or equal to 50 % restenosis) of treated lesions was an additional morphological end-point, assessed by duplex sonography. A total of 74 limbs (73 patients) were treated with DESs and 66 limbs (64 patients) were treated with PTA-BMS. The estimated 5-year major amputation rate was lower in the DES arm (19.3 % versus 34.0 % for PTA-BMS; p = 0.091). The 5-year rates of amputation- and event-free survival (survival free from major amputation or reintervention) were significantly higher in the DES arm compared with PTA-BMS (31.8 % versus 20.4 %, p = 0.043; and 26.2 % versus 15.3 %, p = 0.041, respectively). Survival rates were comparable. The limited available morphological results showed higher preserved patency rates after DESs than after PTA-BMS at 1, 3, and 4 years of follow-up. The investigators concluded that compared to PTA-BMS, clinical and morphological long-term results after treatment of infrapopliteal lesions in patients with critical limb ischemia are improved with DES.

Giaquinta et al (2017) conducted a prospective clinical trial to evaluate if using Xience-Prime Everolimus-Eluting Stent (EES) is an effective treatment for critical limb ischemia and infrapopliteal arterial occlusive disease in patients with Rutherford-Becker category between 4 and 5. Between June 2011 and April 2014, a total of 122 patients with angiographic documented segment P3 of popliteal artery and proximal tibial arteries stenosis greater than
70 %, and lesion length between 20 mm and 100 mm (mean lesion length 52.7 mm), meeting the inclusion criteria, were included in the study. The 1- and 3-year primary patency rates were 88.9 % and 80.1 %, respectively. The survival, major amputation-free survival, and target lesion revascularization rates were 88.1 %, 93 %, and 91.5 % at 1-year and 70.4 %, 89.3 %, and 85.1 % at 3-year follow-up, respectively. Primary patency influenced major amputation rate, which was 60 % in patients with no target artery patency versus 5.4 % in patients with patency (p = .022). At 1-year follow-up, 78 (88.6 %) of 88 patients improved 1 or more of their Rutherford-Becker category, and 48 (80 %) of 69 patients had wound healing. The investigators concluded that their study results suggest that a conservative approach, with EES, appeared feasible in selected patients with CLI and infrapopliteal artery occlusive disease.

According to the 2016 AHA/ACC Lower Extremity PAD guidelines, endovascular techniques to treat claudication include balloon dilation angioplasty, stents, and atherectomy. Techniques continue to evolve and now include covered stents, DES, cutting balloons, and drug-coated balloons. Re-vascularization is performed on lesions that are deemed to be hemodynamically significant. Stenosis of 50 % to 75 % diameter by angiography may not be hemodynamically significant. Resting or provoked intravascular pressure measurements may be used to determine whether lesions are significant. Isolated infrapopliteal disease is unlikely to cause claudication. Incidence of ISR is high and long-term benefit lacking with bare-metal stenting of the infrapopliteal arteries. Studies that have enrolled patients with claudication as well as CLI have demonstrated a benefit of DES versus BMS or versus drug-coated balloons for re-vascularization of infrapopliteal lesions. However, these differences were mainly for patency and restenosis end-points, and neither of these studies included patient-oriented outcomes, such as walking function or QoL parameters. Additional efficacy data on the use of infrapopliteal drug-coated balloon or DES for the treatment of claudication are likely to be published in the near future. In general, the advantages of DES and drug-coated balloons over PTA alone or bare-metal stents are more consistent in the femoropopliteal segment than for infrapopliteal interventions. However, these differences are mainly for patency, restenosis, and repeat-revascularization end-points. Most studies were underpowered or did not examine other patient-oriented outcomes, such as amputation or wound healing in CLI. Endovascular techniques continue to evolve rapidly, and there has been limited literature comparing techniques with regard to clinically significant outcomes, such as amputation or wound healing.

A review in UpToDate on “Percutaneous interventional procedures in the patient with lower extremity claudication” (Zaetta et al, 2017) report that “although PTA in the femoropopliteal segment is associated with restenosis, a clear advantage to primary stenting has not been definitively demonstrated in meta-analyses of randomized trials. In general, longer lesions probably benefit from stenting, but whether a self-expanding metal stent or covered stents should be used remains debated. Local delivery of medical therapies aimed at preventing stenosis using drug-eluting stents has also been tried, as well as the use of biodegradable
stents. The use of drug-eluting stents should be considered experimental therapy”. The authors cited the SIROCCO II trial comparing outcomes of patients with TASC C lesions treated with drug-eluting (sirolimus) versus bare nitinol self-expanding stents (SMART stent). They noted that there were no significant differences in the rates of restenosis between the groups at 2 years (sirolimus group: 22.9 %, bare stent: 21.1 %), and no significant differences for any other variable studied.

An UpToDate review on “Carotid artery stenting and its complications”, (Fairman, 2018) state that “Drug-eluting stents, which are widely used for coronary artery disease, are seldom (if ever) used in the carotid circulation because of the low rate of restenosis with bare metal stents due to the larger diameter of the carotid arteries”.

Henry et al (2005) stated that percutaneous angioplasty and stent placement seem a useful technique for the treatment of vertebro-basilar insufficiency. This technique appears safe and effective for alleviating symptoms and improving blood flow to the cerebral circulation, with a low complications rate and good long-term results. However, this procedure needs experienced interventionists to choose the stent and have appropriate placement of the stent in the ostium of the vertebral artery (VA). The tortuosity of the VA may be technically challenging. The new coronary stents seem to be well-suited to treat atherosclerotic lesions of the origin and of the proximal VA. A large variability of restenosis risk has been reported. Drug-eluting stents may be the solution. The authors stated that prospective, randomized trials are needed to ascertain the clinical effectiveness of VA stenting in stroke prevention, its durability, and to define more clearly its indications.

Chang et al (2017) state that stenosis at the vertebral artery origin is frequent, but associated with low incidence of posterior circulation ischemia. Only 2 % of the patients demonstrate infarction in the posterior circulation, while most of the strokes occur in anterior circulation owing to combined ICA stenosis. The authors cited a recent guideline on secondary stroke prevention, which states that endovascular stenting could be an option in symptomatic extracranial vertebral arterial disease patients refractory to best medical treatment. The authors conducted a case review to evaluate restenosis after stenting in symptomatic vertebral arterial orifice disease. After stenting 11 patients (2 DES, 9 BMS) with symptomatic vertebral arterial orifice stenosis refractory to medical treatment or impairment in anterior circulation, 3 of the 11 patients experienced asymptomatic severe in-stent restenosis or occlusion. Bare metal stents were used in those 3 patients, 2 of whom received revascularization therapy. Development of sufficient cervical collateral channels reconstituting the distal vertebral artery was the common feature in patients with asymptomatic in-stent restenosis. The authors noted that DES significantly reduces restenosis rate to 1/3 of the rate of BMS by preventing neointimal hyperplasia, the cause of which is assumed to be stent restenosis in the second and third case. However, in terms of collateral development, a DES might be inferior to a BMS due to the different pattern of in-stent restenosis and antiarteriogenic effects.
An UpToDate review on “Vertebral artery revascularization” (Morasch, 2017) stated that DES have been tried in the vertebral artery; however, a majority of the studies have mean patient follow-up times less than 1 year, and it remains unclear whether DES will have a significant impact in patients outcomes for those who undergo the vertebral artery intervention.

Vein Graft Stenosis

Vermeersch and Agostoni (2005) noted that the percutaneous treatment of patients with obstructive atherosclerotic disease in degenerated coronary saphenous vein bypass grafts still remains one of the great challenges in interventional cardiology. These researchers discussed the actual evidence-based knowledge for the percutaneous management of this lesion subset, focusing in particular on the devices that are actually considered the “gold standard” for this treatment: BMS and distal protection devices. They commented on the negative results of the randomized trials regarding the promising polytetrafluoroethylene-covered stent-grafts, and offered insights into the currently available evidence for the use of DES in saphenous vein grafts. The authors stated that these devices are potentially the key promise for the long-term successful sealing of vein graft disease; however, clear and definitive data from controlled studies are needed.

In a meta-analysis, Joyal et al (2010) compared DES to BMS for the treatment of vein graft stenosis. PubMed and the Cochrane clinical trials database were systematically searched to identify all RCTs and observational studies examining DES for vein graft stenosis published in English between 2003 and 2009. Inclusion criteria included follow-up duration greater than or equal to 6 months. Data were stratified by study design and pooled using random effects models. A total of 20 studies were found to meet inclusion criteria; 18 studies were observational and 2 were RCTs. In observational studies, DES were associated with a reduction in MACE (odds ratio [OR] 0.50, 95 % CI: 0.35 to 0.72), death (OR 0.69, 95 % CI: 0.53 to 0.91), TVR (OR 0.54, 95 % CI: 0.37 to 0.79), and TLR (OR 0.54, 95 % CI: 0.37 to 0.78). The incidence of MI was similar between groups. In the RCTs, pooled results were inconclusive because of small sample sizes. The authors concluded that although data from observational studies suggest that the use of DES for vein graft stenosis has favorable effects on MACE, death, TVR, and TLR, these data should be interpreted with caution due to their observational nature. Corresponding RCT data are inconclusive. There remains a need for large multi-center RCTs to address the safety and effectiveness of DES for vein graft stenosis.

Venous Stenosis Associated with Dialysis Vascular Access

Athappan and Ponniah (2009) stated that studies on percutaneous transluminal cardiac angioplasty (PTCA) in patients with end stage renal disease (ESRD) on hemodialysis (HD) have suggested high rates of procedural complications and re-stenosis. Bare metal stent
PCI has significantly reduced re-stenosis and subsequent TLR in these patients, although not to the level of non-hemodialysis (NH) controls. The introduction of DES has dramatically reduced re-stenosis rates compared with BMS in patients with various clinical and angiographic characteristics, however their impact on patients with ESRD on dialysis is unclear due to consistent exclusion of this population from major trials. The purpose of this study was therefore to compare the outcomes of PCI with DES and BMS when used for ESRD patients on HD, by meta-analytical techniques. Comparative studies published between January 2002 and January 2009 of DES versus BMS in ESRD patients on dialysis were identified using an electronic search and reviewed using a random effects model. The primary endpoints of this study were the hard endpoints of mortality, MI and TLR. A secondary endpoint of this analysis was late luminal loss. In-hospital mortality and MI were also assessed. Heterogeneity was assessed using Cochrane Q and I(2) statistics. A total of 5 reports comprising 641 patients (279 DES, and 362 BMS) were included in the analysis. All the studies were non-randomized comparisons between DES and BMS. The length of follow-up was in the range between 9 and 12 months. In-hospital clinical outcomes were similar between the 2 groups. At follow-up there was a trend towards lower TLR (OR 0.50, CI: 0.27 to 0.93, p = 0.011 I(2) = 48 %) and decreased late luminal loss (weighted mean difference [WMD] -0.34, CI: -0.58 to 0.10, p = 0.09, I(2) = 58 %) in patients undergoing PCI with implantation of DES. There was no difference in the rates of all-cause mortality (OR 0.66, CI: 0.40 to 1.08, p = 0.070, I(2) = 0 %), and MI (OR 1.35, CI: 0.52 to 3.52, p = 0.53, I(2) = 0 %) between the 2 groups. The authors concluded that in ESRD patients on HD undergoing PCI, DES are safe and reduce repeat revascularizations. Moreover, they noted that the limited number of patients as well as the limited quality of primary studies included need careful interpretation of these results. They stated that further well-designed, large RCTs are needed to establish the strategy of management in ESRD patients undergoing PCI.

The potential superiority of DES over BMS in reducing TLR or TVR in patients with ESRD on HD has not been established. Small studies comparing DES to BMS in this population have yielded inconclusive results mainly due to the small sample size. Abdel-Latif et al (2010) examined the total weight of evidence regarding the use of DES and BMS in patients with ESRD. These investigators searched MEDLINE, EMBASE, Science Citation Index, CINAHL, and the Cochrane CENTRAL database of controlled clinical trials (December 2009) for controlled trials comparing DES to BMS in ESRD patients. They conducted a fixed-effects meta-analysis across 7 eligible studies (n = 869 patients). Compared with BMS-treated patients, DES-treated patients had significantly lower TLR/TVR (OR 0.55 CI: 0.39 to 0.79) and major adverse cardiac events (MACE) (OR 0.54; CI: 0.40 to 0.73). The absolute risk reduction (ARR) with DES in TLR/TVR was -0.09 (CI: -0.14 to -0.04; NNT 11) and in MACE was -0.13 (CI: -0.19 to -0.07; NNT 8). A trend towards lower incidence of all-cause mortality was also noted with DES (OR 0.68; CI: 0.45 to 1.01). No significant differences were noted between the 2 groups in the relative or absolute risk of MI. The authors concluded that the use of DES in patients with ESRD is safe and yields significant...
reduction in the risk of TLR/TVR and MACE. Moreover, they stated that larger RCTs are needed to confirm the results of this meta-analysis and establish the appropriate stent choice in this high-risk population.

Otsuka et al (2011) stated that long-term outcomes after SES implantation in HD patients have remained controversial. These researchers investigated the impact of HD on outcomes after SES implantation. They analyzed the data on 2,050 patients who underwent SES implantation in a multi-center prospective registry in Japan. Three-year clinical outcomes were compared between the HD group (n = 106) and the NH group (n = 1,944). At the 3-year clinical follow-up, the rates of unadjusted cardiac mortality (HD: 16.3 versus NH: 2.3 %) and TLR (HD: 19.4 versus NH: 6.6 %) were significantly higher in the HD group than the NH group (p < 0.001). Although HD group had a numerically higher stent thrombosis rate, the difference in stent thrombosis between the 2 groups (HD: 2.0 versus NH: 0.7 %) did not reach statistical significance. Using Cox's proportional-hazard models with propensity score adjustment for baseline differences, the HD group had higher risks of TLR (HD: 16.3 versus NH: 6.1 %; HR, 2.83; 95 % CI: 1.62 to 4.93, p = 0.0003) and cardiac death (HD: 12.3 versus NH: 2.3 %; HR, 5.51; 95 % CI: 2.58 to 11.78, p < 0.0001). The consistent results of analyses, whether unadjusted or adjusted for other baseline clinical and procedural differences, identify HD as an independent risk factor for cardiac death and TLR. The authors concluded that PCI with SES in HD patients has a higher incidence of repeat revascularization and mortality compared with those in NH patients. Moreover, HD appears to be strongly associated with mortality and repeat revascularization even after SES implantation.

Charytan et al (2011) examined the long-term clinical outcomes following DES or BMS placement in patients with severely reduced glomerular filtration rate (GFR). All adults with chronic kidney disease (CKD) and severely decreased GFR (GFR; serum creatinine greater than 2.0 mg/dL or dialysis dependence) undergoing PCI with stent placement between April 1, 2003, and September 30, 2005, at all acute-care nonfederal hospitals in Massachusetts were included in this analysis. Patients were classified as DES-treated if all stents were drug eluting and BMS-treated if all stents were bare metal. Patients treated with both types of stents were excluded from the primary analysis. 2-year crude mortality risk differences (drug-eluting - bare-metal stents) were determined from vital statistics records, and risk-adjusted mortality, MI, and revascularization differences were estimated using propensity score matching of patients with severely reduced GFR based on clinical and procedural information collected at the index admission. A total of 1,749 patients with severely reduced GFR (24 % dialysis dependent) were treated with DES (n = 1,256) or BMS (n = 493) during the study. Overall 2-year mortality was 32.8 % (unadjusted DES versus BMS; 30.1 % versus 39.8 %; p < 0.001). After propensity score matching 431 patients with a DES to 431 patients with a BMS, 2-year risk-adjusted mortality, MI, and TVR rates were 39.4 % versus 37.4 % (risk difference, 2.1 %; 95 % CI: -4.3 to 8.5; p = 0.5), 16.0 % versus 19.0 % (risk difference, -3.0 %; 95 % CI: -8.2 to 2.1; p = 0.3), and 13.0 % versus 17.6 % (risk difference,
-4.6 %; 95 % CI: -9.5 to 0.3; p = 0.06). The authors concluded that in patients with severely
decreased GFR, treatment with DES was associated with a modest decrease in TVR not
reaching statistical significance and was not associated with a difference in risk-adjusted
rates of mortality or MI at 2 years compared with BMS.

Green et al (2011) examined the safety and effectiveness of DES in patients with CKD not
on renal replacement therapy. Patients were drawn from the National Heart, Lung, and
Blood Institute Dynamic Registry and were stratified by renal function based on estimated
GFR. Of the 4,157 participants, 1,108 had CKD ("low GFR" less than 60 ml/min/1.73 m(2)),
whereas 3,049 patients had normal renal function ("normal GFR" greater than or equal to 60
ml/min/1.73 m(2)). For each stratum of renal function, these investigators compared risk of
death, MI, or repeat revascularization between subjects who received DES and BMS at the
index procedure. Patients with low GFR had higher 1-year rates of death and MI and a
decreased rate of repeat revascularization compared to patients with normal GFR. Use of
DES was associated with a decreased need for repeat revascularization in the normal-GFR
group (adjusted HR 0.63, 95 % CI: 0.50 to 0.79, p <0.001) but not in the low-GFR group (HR 0.69, 95 % CI: 0.45 to 1.06, p = 0.09). Risks of death and MI were not different between the
2 stents in either patient population. The authors concluded that the presence of CKD
predicted poor outcomes after PCI with high rates of mortality regardless of stent type.
Moreover, the effect of DES in decreasing repeat revascularization appeared to be
attenuated in these patients.

Also, an UpToDate review on “Use of stents for venous stenosis associated with dialysis
vascular access” (Beathard, 2013) states that “Although not yet evaluated clinically for
dialysis vascular access, there is preliminary evidence in animals that sirolimus-eluting
stents may provide short-term effectiveness in animal model arteriovenous grafts”.

Bioabsorbable Polymer Stents

Bioabsorbable drug-eluting stents (DES) refers to the incomplete breakdown of material
which may be partially digested and remain indefinitely in local tissue. Stent material and
polymer may be bioabsorbable. The majority of currently approved DES have a durable
polymer, which remains permanently on the stent after the drug is eluted. The polymer itself
may result in vascular inflammation or delay endothelialization and healing, therefore
contributing to the risk of stent thrombosis. The premise of the bioabsorbable polymer stent
is that with the polymer being completely biodegradable, it removes the potential stimulus for
chronic inflammation, and the patient is essentially left with a bare-metal stent (Cutlip and

Ma and colleagues (2012) stated that “Although some non-biodegradable polymer-coated
DES claimed to be safe long-term, there remains caution regarding the inflammatory
response. Thus, biodegradable polymers are being considered and investigated to store
and deliver drugs. The most commonly used polymers now are poly(lactic acid) (PLA), poly (glycolic acid) and their copolymer, poly(lactic-co-glycolic acid) (PLGA), which can be fully degraded and metabolized by the body. A multitude of biodegradable polymer-coated stents are currently in clinical trials. For example, the Sparrow™ NiTi stent system (Surmodics Inc., Eden Prairie, MN, USA) employs SynBiosys™ biodegradable polymer PLGA to elute sirolimus; the CE-approved Biomatrix® stent (Biosensors International, Singapore), which was licensed to Terumo Corporation (Tokyo, Japan) with a new brand name (Nobori®) in May 2007, releases a sirolimus analogue, biolimus A9, from PLA coated on 316L stainless steel stent platform; both Excel® (JW Medical Systems, China) and Cura™ (OrbusNeich Medical, Inc., FL, USA) are PLA and sirolimus-coated stainless steel stents; Conor Medstent™ stent (Conor Medsystems, CA, USA) uses PLGA while Infinnium™ stent (Sahajanand Medical Technologies, India) utilizes PLA to elute paclitaxel. In spite of many promising preliminary results, the development of biodegradable polymers in DES is still a challenge.

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical’ s assessment on “Biodegradable stents” (ASERNIP-S, 2013) considers biodegradable polymer drug eluting stents to be investigational. The authors stated that this assessment of biodegradable polymer stents for coronary artery disease (CAD) was based on a meta-analysis of 10 RCTs, a large RCT and a single-arm registry with 5 years of data. The most rigorous evidence, a recent meta-analysis, found no significant benefit of biodegradable stents for CAD with respect to death, MI or late ST, although benefits were found in rates of TLR and late lumen loss (LLL). The authors postulated that the lack of demonstrated benefit could have been due to heterogeneity among studies for the TLR and LLL outcomes, and variation in types of non-biodegradable DES employed (with most being 1st versus 2nd generation DES). As such, the findings of this meta-analysis cannot be highly weighted. Ideally, future studies should compare stents that utilize the same metal scaffold and anti-proliferative drug, with the only difference being the presence of a durable versus biodegradable polymer, so that the true safety and effectiveness of biodegradable polymer DES can be determined.

Ye and colleagues (2013) noted that DES with biodegradable polymers (BP) have been developed to address the risk of thrombosis associated with 1st-generation DES. These researchers determined the safety and effectiveness of BP biolimus-eluting stents (BP-BES) versus durable polymer (conventional) DES (DP-DES). Systematic database searches of MEDLINE (1950 to June 2013), EMBASE (1966 to June 2013), the Cochrane Central Register of Controlled Trials (Issue 6 of 12, June 2013), and a review of related literature were conducted. All RCTs comparing BP-BES versus DP-DES were included. A total of 8 RCTs investigating 11,015 patients undergoing PCI were included in the meta-analysis. The risk of major adverse cardiac events did not differ significantly between the patients treated with the BP-BES and the DP-DES (RR, 0.970; 95 % CI: 0.848 to 1.111; p=0.662). However, BP-BES was associated with reduced risk of very late ST compared with the DP-
DES, while the risk of early or late ST was similar (RR for early or late ST, 1.167; 95% CI: 0.755 to 1.802; p = 0.487; RR 0.273; 95% CI: 0.115 to 0.652; p = 0.003; p for interaction = 0.003). The authors concluded that in this meta-analysis of RCTs, treatments with BP-BES did not significantly reduce the risk of major adverse cardiac events, but demonstrated a significantly lower risk of very late ST when compared to DP-DES. They stated that this conclusion requires confirmation by further studies with long-term follow-up.

Palmerini and associates (2014) examined the relative safety and effectiveness of bioabsorbable polymer-based BES versus DP-DES and DP-BMS by means of a network meta-analysis. Randomized controlled trials comparing bioabsorbable polymer-BES versus currently U.S.-approved DES or BMS were searched through MEDLINE, EMBASE, and Cochrane databases. Information on study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted. Data from 89 trials including 85,490 patients were analyzed. At 1-year follow-up, bioabsorbable polymer-BES were associated with lower rates of cardiac death/MI, MI, and TVR than BMS and lower rates of TVR than fast-release zotarolimus-eluting stents. The bioabsorbable polymer-BES had similar rates of cardiac death/MI, MI, and TVR compared with other 2nd-generation DP-DES but higher rates of 1-year ST than cobalt-chromium everolimus-eluting stents (CoCr-EES). The bioabsorbable polymer-BES were associated with improved late outcomes compared with BMS and paclitaxel-eluting stents, considering the latest follow-up data available, with nonsignificantly different outcomes compared with other DP-DES although higher rates of definite ST compared with CoCr-EES. The authors concluded that in this large-scale network meta-analysis, bioabsorbable polymer-BES were associated with superior clinical outcomes compared with BMS and 1st-generation DES and similar rates of cardiac death/MI, MI, and TVR compared with 2nd-generation DP-DES but higher rates of definite ST than CoCr-EES.

Zhang (2014) noted that delayed re-endothelialization may be the pathophysiological cause of ST. Biodegradable polymer DES (BP-DES) may reduce the risk of ST. These investigators evaluated the risk of ST in patients treated with BP-DES. Studies were retrieved from the PubMed, Cochrane Library, and EMBASE online databases. A total of 12 studies (15,155 patients) with long-term follow-up (greater than or equal to 12 months) were included. Compared with DP-DES, BP-DES did not significantly decrease the risk of definite and probable ST (RR, 0.89; 95% CI: 0.68 to 1.18; p = 0.425) and definite ST (RR, 0.92; 95% CI: 0.66 to 1.30; p = 0.648). Furthermore, there was no difference in the risk of late ST (RR, 1.17; 95% CI: 0.39 to 3.53; p = 0.780). However, the rate of early ST was slightly higher in the BP-DES group (RR, 1.60; 95% CI: 0.94 to 2.73; p = 0.084) than in the DP-DES group. A significant reduction in very late ST (greater than 12 months) was evident with the BP-DES group (RR, 0.27; 95% CI: 0.10 to 0.68; p = 0.006). Subgroup analysis showed that there was no difference in the rate of definite and probable ST between the BP-DES and

1st- or 2nd-generation DES groups. The authors concluded that biodegradable polymer stents were associated with a significantly lower risk of very late ST. However, there was no difference in the risk of definite and probable ST between the 2 groups.

Wang and colleagues (2014) stated that BP-DES represent a promising strategy to improve the delayed healing and hypersensitive reaction in the vessel. However, the safety and effectiveness of BP-DES versus permanent polymer DES (PP-DES) are less well-defined. In a meta-analysis, these researchers compared the total, short (less than 30 days), mid (30 days to 1 year) and long (greater than 1 year) term outcomes of BP-DES versus PP-DES. PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for RCTs to compare any of approved BP- and PP-DES. Effectiveness end-points were TLR and in-stent late loss (ISLL). Safety end-points were death, MI, and composite of definite and probable ST. The meta-analysis included 19 RCTs (n = 18,395) with interesting results. As compared with DES, there was a significantly reduced very late ST (OR [95 % CI]: 0.42 [0.24 to 0.77], p = 0.852) and ISLL (OR [95 % CI]: -0.07 [-0.12 to 0.02], p = 0.000) in BP-DES patients. However, there were no differences between BP-DES and PP-DES for other safety and effectiveness outcomes, except that the stratified analysis showed a significant decreased TLR with BP-DES as compared to paclitaxel-eluting stent (OR [95 % CI]: 0.41 [0.20 to 0.81], p = 0.457). The authors concluded that BP-DES are more effective in reducing very late ST and ISLL, as well as comparable to PP-DES with regard to death, TLR and MI. Moreover, they stated that further large RCTs with long-term follow-up are needed to better define the relative merits of BP-DES.

Kwong and Yu (2014) systematically reviewed the latest randomized evidence on the safety and effectiveness of BP-DES as compared to DP-DES. MEDLINE, Embase, and the Cochrane database were searched in August 2013 for eligible RCTs comparing BP-DES with DP-DES. Clinical outcomes of interest were mortality, MI, TLR, TVR, and ST. A total of 20 RCTs randomizing 20,021 participants were included, of whom 11,045 were allocated to BP-DES and 8,976 to DP-DES. Treatment of BP-DES was not associated with a significant reduction of any of the clinical outcomes (all-cause mortality, OR: 0.94, 95 % CI: 0.80 to 1.10, p = 0.42; cardiovascular mortality, OR: 0.97, 95 % CI: 0.79 to 1.19, p = 0.74; MI, OR: 1.07, 95 % CI: 0.91 to 1.26, p = 0.41; TLR, OR: 0.87, 95 % CI: 0.69 to 1.08, p = 0.20; TVR, OR: 1.05, 95 % CI: 0.85 to 1.28, p = 0.67; definite/probable ST, OR: 0.80, 95 % CI: 0.59 to 1.07, p = 0.14). The authors concluded that current randomized data indicate that clinical safety and effectiveness profiles of BP-DES are comparable to those of DP-DES. Moreover, they stated that findings from large-scale studies with rigorous methodology and long follow-up duration are needed.

Niu and co-workers (2014) compared the short- and long-term outcomes and the ST risk in patients treated with BP-DES versus PP-DES. These investigators searched Medline, Embase, Web of science, CENTRAL databases, and conference proceedings/abstracts for RCTs comparing BP-DES with PP-DES. The primary end-point was to compare the risks of
overall and different temporal categories definite/probable ST. Other clinical outcomes were TLR, MI, and all-cause death in short-term (less than or equal to 1 year) and long-term follow-up. The meta-analyses were performed by computing ORs with 95 % CIs using a random-effects model. A total of 19 RCTs including 20,229 patients were analyzed. Overall, BP-DES significantly decreased the risks of very late definite/probable ST (OR 0.33; 95 % CI: 0.16 to 0.70), and TLR in long-term follow-up (OR 0.70; 95 % CI: 0.52 to 0.95) compared with PP-DES. There were no significant differences between the groups regarding MI incidence and mortality during both short- and long-term follow-up period. In stratified analyses, the long-term superiority of BP-DES was only maintained by using 1st-generation DES as the comparators. The authors concluded that the present meta-analysis indicated that BP-DES were more effective than PP-DES at reducing the risks of very late ST and long-term TLR, but it could vary by heterogeneities in the use of PP-DES comparators. Moreover, they stated that additional rigorous RCTs with longer follow-up periods are needed to verify these very promising long-term end-points.

Pilgrim et al (2014) compared the safety and effectiveness of a novel, ultrathin strut cobalt-chromium stent releasing sirolimus from a biodegradable polymer with a thin strut durable polymer everolimus-eluting stent. These researchers performed a randomized, single-blind, non-inferiority trial with minimum exclusion criteria at 9 hospitals in Switzerland. They randomly assigned (1:1) patients aged 18 years or older with chronic stable CAD or acute coronary syndromes undergoing PCI to treatment with biodegradable polymer sirolimus-eluting stents or durable polymer everolimus-eluting stents. Randomization was via a central web-based system and stratified by center and presence of ST segment elevation MI. Patients and outcome assessors were masked to treatment allocation, but treating physicians were not. The primary end-point, target lesion failure, was a composite of cardiac death, target vessel MI, and clinically-indicated target lesion re-vascularization at 12 months. A margin of 3.5 % was defined for non-inferiority of the biodegradable polymer sirolimus-eluting stent compared with the durable polymer everolimus-eluting stent. Analysis was by intention-to-treat. Between February 24, 2012, and May 22, 2013, these investigators randomly assigned 2,119 patients with 3,139 lesions to treatment with sirolimus-eluting stents (1,063 patients, 1,594 lesions) or everolimus-eluting stents (1,056 patients, 1,545 lesions). A total of 407 (19 %) patients presented with ST-segment elevation MI. Target lesion failure with biodegradable polymer sirolimus-eluting stents (69 cases; 6.5 %) was non-inferior to durable polymer everolimus-eluting stents (70 cases; 6.6 %) at 12 months (absolute risk difference -0.14 %, upper limit of 1-sided 95 % CI: 1.97 %, p for non-inferiority < 0.0004). No significant differences were noted in rates of definite stent thrombosis (9 [0.9 %] versus 4 [0.4 %], rate ratio [RR] 2.26, 95 % CI: 0.70 to 7.33, p = 0.16). In pre-specified stratified analyses of the primary endpoint, biodegradable polymer sirolimus-eluting stents were associated with improved outcome compared with durable polymer everolimus-eluting stents in the subgroup of patients with ST-segment elevation myocardial infarction (7 [3.3 %] versus 17 [8.7 %], RR 0.38, 95 % CI: 0.16 to 0.91, p = 0.024, p for interaction = 0.014). The authors concluded that in a patient population with minimum
exclusion criteria and high adherence to dual anti-platelet therapy, biodegradable polymer sirolimus-eluting stents were non-inferior to durable polymer everolimus-eluting stents for the combined safety and effectiveness outcome target lesion failure at 12 months. Moreover, they stated that the noted benefit in the subgroup of patients with ST-segment elevation myocardial infarction needs further study.

In a meta-analysis, Lv and colleagues (2015) evaluated the safety and effectiveness of BP-DESs. PubMed, Science Direct, China National Knowledge Infrastructure, and Chongqing VIP databases were searched for RCTs comparing the safety and effectiveness of BP-DESs versus DP-DESs. Effectiveness included the prevalence of TLR, TVR, and LLL, and safety of these stents at the end of follow-up for the selected research studies were compared. A total of 16 qualified original studies that addressed a total of 22,211 patients were included in this meta-analysis. In regard to effectiveness, no statistically significant difference in TLR (OR = 0.94, p = 0.30) or TVR (OR 1.01, p = 0.86) was observed between patients treated with BP-DESs and those with DP-DESs. However, there were significant differences in instent LLL (WMD = -0.07, p = 0.005) and in-segment LLL (WMD = -0.03, p = 0.05) between patients treated with BP-DESs and with DP-DESs. In terms of safety, there was no significant difference in overall mortality (OR 0.97, p = 0.67), cardiac death (OR 0.99, p=0.90), early stent thrombosis (ST) and late ST (OR 0.94, p = 0.76; OR 0.96, p = 0.73), or MI (OR 0.99, p = 0.88) between patients treated with BP-DESs and with DP-DESs. However, there was a statistically significant difference in very late ST (OR 0.69, p = 0.007) between these 2 groups. In addition, the general trend of the rates of TVR and TLR of BP-DESs groups was lower than DP-DESs groups after a 1-year follow-up. The authors concluded that BP-DESs are safe, efficient, and exhibit superior performance to DP-DESs with respect to reducing the occurrence of very late ST and LLL. The general trend of the rates of TVR and TLR of BP-DESs groups was lower than DP-DESs groups after a 1-year follow-up. Moreover, these investigators stated that the follow-up periods of the studies examined in this investigation ranged from 6 to 48 months. To incorporate additional clinical studies with long follow-up times into meta-analyses of this topic and thereby obtain more stable and reliable conclusions, it is necessary to conduct additional large-scale rigorous RCTs with lengthy follow-up durations. Furthermore, they noted that this meta-analysis exhibited the following limitations:

(i) the included studies did not have identical follow-up periods; instead, the range of follow-up durations was relatively broad (between 6 and 48 months), and (ii) the limitations of the meta-analytical approach are well known and documented; thus, the safety and effectiveness of various types of stents was not specifically identified.

Gao and colleagues (2015) evaluated the safety and effectiveness of the novel abluminal groove-filled biodegradable polymer-coated sirolimus-eluting FIREHAWK stent (MicroPort Medical, Shanghai, China) in a large cohort of patients. Trials on the FIREHAWK stent allowing targeted sirolimus release were not individually powered to reliably estimate low-
frequency safety end-points such as stent thrombosis (ST) or to examine long-term safety and effectiveness. Additionally, the China FDA requires an objective performance criterion (OPC) study for new drug-eluting stents. The primary end-point, target lesion failure (TLF), was defined as the composite of cardiac death, target vessel MI, or clinically indicated TLR at 12 months. Patient-level data from 1,007 patients with de-novo native coronary lesions exclusively treated with the FIREHAWK stent in the TARGET serial studies (I and II) were prospectively collected, pooled and analyzed throughout a 2-year follow-up. The 12-month rate of TLF in 1,003 patients (follow-up rate of 99.6 %) was 3.9 % (upper 95 % CI: 5.3 %), which was significantly lower than the performance goal of 9.0 % (p < 0.0001). The 24-month rates of TLF, PoCE (a composite of all-cause death, all MI, or any re-vascularization), and ARC definite or probable ST were 4.6 %, 7.8 % and 0.1 %, respectively. In subgroup analysis, long lesion (greater than or equal to 30 mm) was an independent predictor of TLF within 2 years (HR: 2.44; 95 % CI: 1.32 to 4.53, p < 0.01). The authors concluded that this pooled, patient-level analysis indicated that the FIREHAWK stent exhibits a promising 2-year safety and effectiveness profile.

Zhu and colleagues (2015) noted that durable polymer SES (DP-SES) are associated with a low risk of stent thrombosis; BP-DES were designed to reduce these risks. However, their benefits are still variable. These investigators undertook a meta-analysis of randomized trials identified by systematic searches of Medline, Embase, and the Cochrane Database. A total of 11 studies (9,676 patients) with a mean follow-up of 22.6 months were included. Overall, compared with DP-SES, BP-DES significantly lowered the rate of definite or probable stent thrombosis (RR, 0.73; 95 % CI: 0.55 to 0.97; p = 0.03; I(2) = 0.0 %) due to a decreased risk of very late stent thrombosis (RR, 0.26; 95 % CI: 0.11 to 0.63; p = 0.00; I(2) = 0.0 %). However, BP-DES were associated with a comparable rate of early and late stent thrombosis. Meanwhile, BP-DES were associated with a broadly equivalent risk of TVR (RR, 0.90; 95 % CI: 0.78 to 1.03; p = 0.13; I(2) = 0.0 %), cardiac death (RR, 0.89; 95 % CI: 0.72 to 1.09; p = 0.24; I(2) = 0.0 %), MI (RR, 1.03; 95 % CI: 0.84 to 1.26; p = 0.79; I(2) = 0.0 %), and MACE (RR, 0.91; 95 % CI: 0.83 to 1.0; p = 0.08; I(2) = 0.0 %). Furthermore, angiographic data showed that in-stent and in-segment late luminal loss were similar between the 2 groups. The authors concluded that compared with DP-SES, BP-DES were associated with a lower rate of very late stent thrombosis and an equivalent risk of MACE. Moreover, they stated that larger randomized studies are needed to confirm this finding.

Kereiakis et al (2015) performed a multi-center, randomized controlled trial for regulatory approval to determine noninferiority of the Synergy stent to the durable polymer Promus Element Plus everolimus-eluting stent. Patients (n = 1,684) scheduled to undergo PCI for non-ST-segment-elevation acute coronary syndrome or stable CAD were randomized to receive either the Synergy stent or the Promus Element Plus stent. The primary end-point of 12-month target lesion failure was observed in 6.7 % of Synergy and 6.5 % Promus Element Plus treated subjects by intention-to-treat (p = 0.83 for difference; p = 0.0005 for non-inferiority), and 6.4 % in both the groups by per-protocol analysis (p = 0.0003 for non-
inferiority). Clinically indicated revascularization of the target lesion or definite/probable ST were observed in 2.6 % versus 1.7 % (p = 0.21) and 0.4 % versus 0.6 % (p = 0.50) of Synergy versus Promus Element Plus-treated subjects, respectively. The authors concluded that, in this randomized trial, the Synergy bioabsorbable polymer everolimus-eluting stent was non-inferior to the Promus Element Plus everolimus-eluting stent with respect to 1-year target lesion failure. The investigators stated that these data support the relative safety and efficacy of Synergy in a broad range of patients undergoing PCI.

In October 2015, the FDA approved the Boston Scientific Synergy Everolimus-Eluting Platinum Chromium Coronary Stent System. The Synergy stent is a thin-strut, platinum chromium metal alloy platform with an ultrathin bioabsorbable Poly(D,L-lactide-co-glycolide) abluminal everolimus-eluting polymer. The EVOLVE II study supported its noninferiority to other drug-eluting stents. “The EVOLVE II trial randomized 1684 patients with stable angina or non-ST segment elevation acute coronary syndrome to the SYNERGY stent or durable polymer platinum chromium EES. The primary end point of 12-month target lesion failure was observed in 6.7 percent of SYNERGY and 6.5 percent durable polymer EES-treated subjects (p = 0.83 for difference; p = 0.0005 for noninferiority). Clinically indicated target lesion revascularization or stent thrombosis were observed in 2.6 versus 1.7 percent (p = 0.21) and 0.4 versus 0.6 percent (p = 0.50) of SYNERGY versus PROMUS Element Plus-treated subjects, respectively” (Cutlip and Abbott, 2017). The bioabsorbable polymer is fully absorbed between three and four months. While existing DES devices reduce coronary restenosis, the polymer remains on the stent after the drug is delivered. Long-term exposure to the polymer may cause inflammation, which delays healing and has been associated with complications, including neoatherosclerosis and stent thrombosis. The Synergy Stent is designed for faster and sustained healing by eliminating long term polymer exposure.

Buccheri and colleagues (2019) noted that randomized clinical trials have consistently demonstrated the non-inferiority of bioabsorbable polymer DES (BP-DES) with respect to DES having permanent polymers (PP-DES). To-date, the comparative performance of BP- and PP-DES in the real world has not been extensively investigated. From October 2011 to June 2016, these researchers analyzed the outcomes associated with newer generation DES use in Sweden. After stratification according to the type of DES received at the index procedure, a total of 16,504 and 79,106 stents were included in the BP- and PP-DES groups, respectively. The Kaplan-Meier estimates for re-stenosis at 2 years were 1.2 % and 1.4 % in BP- and PP-DES groups, respectively. Definite stent thrombosis (ST) was low in both groups (0.5 % and 0.7 % in BP- and PP-DES groups, respectively). The adjusted HR for either re-stenosis or definite ST did not differ between BP- and PP-DES [adjusted HR 0.95, 95 % CI: 0.74 to 1.21; p = 0.670 and adjusted HR 0.79, 95 % CI: 0.57 to 1.09; p=0.151, respectively]. Similarly, there were no differences in the adjusted risk of all-cause death and MI between the 2 groups (adjusted HR for all-cause death 1.01, 95 % CI: 0.82 to 1.25; p = 0.918 and adjusted HR for MI 1.05, 95 % CI: 0.93 to 1.19; p = 0.404). The authors
concluded that in a large, nationwide, and unselected cohort of patients, PCI with BP-DES implantation was not associated with an incremental clinical benefit over PP-DES use at 2 years follow-up.

**Bioresorbable Stents**

Bioresorbable stents, or scaffolds, refers to stents and polymers that are fully biodegradable, a complete breakdown and removal of a material over time (Cutlip and Abbott, 2017).

An UpToDate review on “Coronary artery stent types in development” (Cutlip and Abbott, 2014) states that “The coronary stents currently available are permanent implants composed of a metallic alloy. Drug-eluting stents (DES) have additional durable polymer and anti-restenotic drug components. While bare metal stents (BMS) and DES have improved outcomes for patients, they have several limitations. The development of stent thrombosis after placement of BMS or DES and the residual rate of restenosis after DES are two reasons for the development of newer coronary artery stents. This topic will present studies of coronary artery stent types that show promise for reduction in rates of these adverse outcomes, including DES with bioresorbable polymers vascular scaffolds. The terms bioresorbable (also called biodegradable) and bioabsorbable are used in this topic. Bioresorbable refers to the complete breakdown and removal of a material over time and often by a known mechanism. Bioabsorbable refers to incomplete breakdown; the material may be partially digested and remain indefinitely in local tissue. Stent material and polymer may be bioresorbable or bioabsorbable …. Newer stent types are being developed to overcome some of the limitations of current stents, such as the development of stent thrombosis after placement of any intracoronary stent and the residual rate of restenosis after drug-eluting stent (DES). These newer stent types fall into three broad categories: stents with bioresorbable polymer; drug-eluting stents that are polymer free; or stents with a bioresorbable scaffold”.

Zhang and colleagues (2016) estimated the incidence of stent thrombosis after everolimus-eluting bioresorbable vascular scaffold (BVS) implantation and compared the safety and effectiveness of BVSs versus EESs in adults having PCI. Data sources included PubMed, Embase, Cochrane Central Register of Controlled Trials, conference proceedings, and relevant Web sites from inception through January 20, 2016. A total of 6 RCTs and 38 observational studies, each involving at least 40 patients with BVS implantation were included in this analysis. Two reviewers independently extracted study data and evaluated study risk of bias. The pooled incidence of definite or probable stent thrombosis after BVS implantation was 1.5 events per 100 patient-years (PYs) (95 % CI: 1.2 to 2.0 events per 100 PYs) (126 events during 8,508 PYs). Six randomized trials that directly compared BVSs with EESs showed a non-statistically significant increased risk for stent thrombosis (OR, 2.05 [CI: 0.95 to 4.43]; p = 0.067) and MI (OR, 1.38 [CI: 0.98 to 1.95]; p = 0.064) with BVSs. The 6 observational studies that compared BVSs with EESs showed increased risk for stent...
thrombosis (OR, 2.32 [CI: 1.06 to 5.07]; p = 0.035) and MI (OR, 2.09 [CI: 1.23 to 3.55]; p = 0.007) with BVSs. The relative rates of all-cause and cardiac death, re-vascularization, and target lesion failure were similar for BVSs and EESs. The authors concluded that compared with EESs, BVSs did not eliminate and might increase risks for stent thrombosis and MI in adults having PCI. Moreover, they stated that results of large trials with long-term follow-up are needed to establish the safety or at least the non-inferiority of BVSs compared with EESs.

In an editorial that accompanied the afore-mentioned study by Zhang et al, Martin and Hasan (2016) stated that “although this is a major stride for BVS and the Absorb stent, the device is still in the early stage, and long-term post-marketing surveillance will be needed to ensure both safety and efficacy in broader populations”.

Mahmoud and associates (2017) stated that data regarding the long-term safety and effectiveness of everolimus-eluting BVS compared with EESs are limited. These researchers performed a meta-analysis to compare the long-term outcomes with both devices. Randomized trials reporting clinical outcomes beyond 1 year and comparing BVS with EESs were included. Summary estimates RRs were constructed. The primary efficacy outcome was target lesion failure, defined as CD, target vessel MI (TV-MI), and ischemia-driven TLR, and the primary safety outcome was definite or probable stent/scaffold thrombosis. A total of 6 trials with 5,392 patients were included (mean follow-up of 25 months); BVS had a higher rate of target lesion failure (RR, 1.33; 95 % CI: 1.11 to 1.58) driven by the higher rates of TV-MI (RR, 1.65; 95 % CI: 1.26 to 2.17) and TLR (RR, 1.39; 95 % CI: 1.08 to 1.78). The risk of definite or probable stent/scaffold thrombosis (RR, 3.22; 95 % CI: 1.89 to 5.49) and very late stent/scaffold thrombosis (greater than 1 year; RR, 4.78; 95 % CI: 1.66 to 13.8) was higher with BVS. The risk of CD and all-cause mortality was similar in both groups. The authors concluded that compared with EESs, BVS is associated with increased risk of target lesion failure driven by the increased rates of TV-MI and ischemia-driven TLR in these studies (mean follow-up of 25 months). The risk of definite or probable stent/scaffold thrombosis and very late stent/scaffold thrombosis appeared to be higher with BVS. They stated that further information from randomized trials is needed to assess clinical outcomes with BVS on complete resolution of the scaffold.

Nairoz and colleagues (2017) noted that data regarding long-term clinical outcomes with everolimus-eluting BVS versus 2nd-generation DES are scarce. These investigators searched online databases until October 2016 for studies comparing BVS versus DES reporting outcomes at 2-year follow-up. They performed a meta-analysis comparing BVS with DES across the spectrum of CAD. Random effects model OR was calculated for outcomes of interest including device-oriented composite events (DOCE; defined as composite of CD, TV-MI, and ischemia-driven TLR), all-cause mortality, definite ST, TV-MI and TLR. A total of 2,360 patients enrolled in 5 studies met inclusion criteria in this analysis. At 2-year follow-up, BVS was associated with higher rates of DOCE (6.9 % versus
4.5 %, OR = 1.53; 95 % CI: 1.06 to 2.23; p = 0.02), absolute risk increase (ARI) 2.4 %, relative risk increase (RRI) 53 %, TV-MI (4 % versus 1.8 %, OR = 1.94; 95 % CI: 1.02 to 3.67; p = 0.04), ARI 2.2 %, RRI 122 % and definite ST (2.1 % versus 0.6 %, OR = 3.39; 95 % CI: 1.46 to 7.88; p = 0.005), ARI 1.5 %, RRI 250 % compared with DES. No differences in all-cause mortality (OR = 0.86; 95 % CI: 0.26 to 2.81; p = 0.80) and TLR (OR = 1.44; 95 % CI: 0.81 to 2.54; p = 0.21) were observed between the 2 groups. The authors concluded that BVS may be associated with worse long-term clinical outcomes compared with DES. They stated that randomized clinical trials are needed to ascertain long-term safety and effectiveness of BVS and identify predictors of adverse events (AEs) with BVS compared with DES.

On March 18, 2017, the FDA informed health care providers treating patients with Absorb GT1 BVS that there is an increased rate of MACE observed in patients receiving the BVS, when compared to patients treated with the approved metallic XIENCE DES. The FDA’s initial review of 2-year data from the BVS pivotal clinical study (the ABSORB III Trial) showed an 11 % rate of MACE (e.g., CD, heart attack, or the need for an additional procedure to re-open the treated heart vessel) in patients treated with the BVS at 2 years, compared with 7.9 % in patients treated with the already-approved Abbott Vascular’s metallic XIENCE DES (p = 0.03). This study also showed a 1.9 % rate of developing ST within the BVS versus 0.8 % within the XIENCE stent at 2 years. These observed higher MACE rates in BVS patients were more likely when the device was placed in small heart vessels. The FDA is working with Abbott Vascular, Inc. to conduct additional analyses to better understand the cause(s) of the higher cardiac event and device thrombosis rates in patients treated with BVS compared to the XIENCE stent. The FDA will continue to monitor the performance of the BVS in ongoing clinical studies and in reports submitted to FDA through MedWatch.

Cassese et al (2016) conducted a meta-analysis to assess the efficacy and safety of everolimus-eluting BVSs versus everolimus-eluting metallic stents in patients with ischaemic heart disease treated with percutaneous revascularisation. The authors searched Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific sessions abstracts, and relevant websites for randomized trials investigating everolimus-eluting BVSs versus everolimus-eluting metallic stents published or posted between Nov 30, 2006, and Oct 12, 2015. The primary efficacy outcome was TLR and the primary safety outcome was definite or probable stent (scaffold) thrombosis. Secondary outcomes were target lesion failure (the composite of cardiac death, target-vessel myocardial infarction, or ischaemia-driven target lesion revascularisation), myocardial infarction, death, and in-device late lumen loss. The authors derived ORs and weighted mean differences with 95 % CIs, and calculated the risk estimates for the main outcomes according to a random-effects model. The authors included 6 trials, comprising data for 3,738 patients randomized to receive PCI with either an everolimus-eluting BVS (n = 2,337) or an everolimus-eluting metallic stent (n = 1,401). Median follow-up was 12 months (inter-quartile range [IQR] 9 to 12). Patients
treated with BVSs had a similar risk of TLR (OR 0.97 [95 % CI: 0.66 to 1.43]; p = 0.87),
target lesion failure (1.20 [0.90 to 1.60]; p = 0.21), MI (1.36 [0.98 to 1.89]; p = 0.06), and
death (0.95 [0.45 to 2.00]; p = 0.89) as those treated with metallic stents. Patients treated
with a BVS had a higher risk of definite or probable ST than those treated with a metallic
stent (OR 1.99 [95 % CI: 1.00 to 3.98]; p = 0.05), with the highest risk between 1 and 30
days after implantation (3.11 [1.24 to 7.82]; p = 0.02). Lesions treated with a BVS had
greater in-device late lumen loss than those treated with a metallic stent (weighted mean
difference 0.08 [95 % CI 0.05 to 0.12]; p < 0.0001). The authors concluded that, compared
with everolimus-eluting metallic stents, everolimus-eluting BVSs had similar rates of repeat
revascularization at 1 year of follow-up, despite inferior mid-term angiographic performance.
However, patients treated with a BVS had an increased risk of subacute ST. Studies with
extended follow-up in a larger number of patients are needed to fully assess the long-term
advantages of everolimus-eluting BVSs.

An accompanying editorial (Finn and Vermani, 2016) stated that “[t]he most striking and
important findings [of Cassese and colleagues] concern the issue of stent thrombosis, which
was more than twice as prevalent in patients with bioresorbable vascular scaffolds than in
those with metallic stents. Many of the events occurred within the first 30 days despite
optimal compliance with dual antiplatelet therapy. Although we are not informed as to the
exact causes of thrombosis, the limitations of bioresorbable vascular scaffolds in terms of
impaired endothelial cell coverage, and potential issues involving implantation techniques or
scaffold integrity, are key issues to focus on to improve understanding of why relatively early
thrombosis is increased. Perhaps equally important is whether at longer-term follow-up the
apparent weaknesses of the bioresorbable vascular scaffold design, including prolonged
degradation time and late inflammation with bulky struts, predispose the patient to late
thrombotic events”.

An assessment by the National Institute for Health and Care Excellence (2016) found: “The
evidence suggests that the risks of death, myocardial infarction and target lesion failure are
similar for Absorb BVS, bare-metal stents and metallic drug-eluting stents at up to
12 months’ follow-up. Stent thrombosis (definite or probable) was more frequent and
medium-term in-device and in-segment lumen loss was greater with Absorb BVS than with
some second-generation metallic drug-eluting stents. Key uncertainties around the
evidence are about longer-term outcomes associated with the Absorb BVS compared with
metallic drug-eluting stents. NICE interventional procedures guidance recommends that
bioresorbable stent implantation should only be used with special arrangements for clinical
governance, consent and audit or research”.

Lu and associates (2017) noted that BP-BES are 3rd-generation DES composed of
biodegradable polymers that may improve prognosis after PCI. After 5 years of follow-up,
BP-BES showed conflicting results compared to DP-DES. These investigators performed a
meta-analysis of the outcomes of studies on BP-BES and DP-DES after PCI at 5 years of
follow-up. Eligible studies were retrieved from PubMed, Embase and the Cochrane Library and reported the results of all-cause mortality, MI, TLR, TVR and ST at 5 years of follow-up. A total of 5 studies (4,687 patients) were included in the meta-analysis. At 5 years of follow-up, BP-BES was associated with lower rates of MACE (OR = 0.83, 95 % CI: 0.71 to 0.97), TLR (OR = 0.77, 95 % CI: 0.62 to 0.96) and ST (OR = 0.60, 95 % CI: 0.43 to 0.84), whereas no significant differences in mortality, MI, or TVR rates were detected. The authors concluded that these findings showed that at 5 years of follow-up, BP-BES could significantly reduce the risk of MACE, TLR and ST, which indicated that safety and efficacy were increased after PCI.

The authors stated that this study had several drawbacks. First, only English language articles were included in this study, which may bias the results. Second, patient heterogeneity and confounding factors might have affected the analysis. Third, significant heterogeneity was detected in some pooled analyses, which may have affected the meta-analysis results, even though these researchers adopted the random effects model or introduced sensitivity analysis. Fourth, the number of included studies was relatively small (5 studies). They stated that the results should be interpreted with caution; further studies are needed to confirm these results.

Bundhun and colleagues (2017) systematically compared BP-DES with the 1st-generation DP-DES using a large number of randomized patients. Electronic databases were searched for RCTs comparing BP-DES with 1st-generation DP-DES. The main end-points were the long-term (greater than or equal to 2 years) adverse clinical outcomes that were reported with these 2 types of DES. These researchers calculated ORs with 95 % CIs and the analysis was carried out by RevMan 5.3 software. A total of 12 trials with a total number of 13,480 patients (7730 and 5,750 patients were treated by BP-DES and 1st-generation DP-DES, respectively) were included. During a long-term follow-up period of greater than or equal to 2 years, mortality, MI, TLR, and MACEs were not significantly different between these 2 groups with OR: 0.84, 95 % CI: 0.66 to 1.07; p=0.16, I=0 %, OR: 1.01, 95 % CI: 0.45 to 2.27; p=0.98, I=0 %, OR: 0.91, 95 % CI: 0.75 to 1.11; p=0.37, I=0 % and OR: 0.86, 95 % CI: 0.44 to 1.67; p=0.65, I=0 %, respectively. Long-term total ST, definite ST, and probable ST were also not significantly different between BP-DES and the 1st-generation DP-DES with OR: 0.77, 95 % CI: 0.50 to 1.18; p=0.22, I=0 %, OR: 0.71, 95 % CI: 0.43 to 1.18; p=0.19, I=0 % and OR: 1.31, 95 % CI: 0.56 to 3.08; p=0.53, I=6 %, respectively. The authors concluded that long-term mortality, MI, TLR, MACEs, and ST were not significantly different between BP-DES and the 1st-generation DP-DES. However, the follow-up period was restricted to only 3 years in this analysis.

This study had several drawbacks. First, due to the limited number of patients, the results of this analysis might be restricted in certain ways. Moreover, the long-term follow-up period was restricted to only 3 years. Further studies with longer follow-up periods would have been more interesting. Unfortunately, data with even longer follow-up periods were not
available. In addition, MACEs were reported in only a few trials. Thus, only a few trials were included in the subgroup analysis of long-term MACEs. This could also represent another drawback of this analysis. Also, the subgroup analyzing total ST included a combination of different types of ST with different definitions. However, heterogeneity was not observed, as most STs, which were reported, were definite and probable ST as defined by the Academic Research Consortium (ARC) classification. In addition, the inclusion of a variety of patients with stable chronic CAD, unstable CAD (ST segment elevation MI and non-ST segment elevated MI) could also represent a limitation of this study. In addition, the duration of dual anti-platelet agents might also have had an effect on the results that were obtained.

Sotomi and co-workers (2017) stated that in the era of DES, large-scale RCTs and all-comer registries have shown excellent clinical results. However, even the latest-generation DES has not managed to address all the limitations of permanent metallic coronary stents, such as the risks of TLR, neo-atherosclerosis, preclusion of late lumen enlargement, and the lack of reactive vasomotion. Furthermore, the risk of very late stent, although substantially reduced with newer-generation DES, still remains. These problems were anticipated to be solved with the advent of fully biodegradable devices. Fully bioresorbable coronary scaffolds have been designed to function transiently to prevent acute recoil, but have retained the capability to inhibit neointimal proliferation by eluting immunosuppressive drugs. Nevertheless, long-term follow-up data of the leading bioresorbable scaffold (BRS; Absorb) are becoming available and have raised a concern about the relatively higher incidence of scaffold thrombosis. To reduce the rate of clinical events, improvements in the device, as well as implantation procedure, are being evaluated. The authors summarized the current limitations of bioresorbable scaffold and their possible solutions. They noted that currently, BRS materials have 3 primary limitations:

- Insufficient ductility, which impacts scaffold retention on balloon catheter and limits the range of scaffold expansion during deployment;
- Low tensile strength and stiffness, which require that struts be thick to prevent recoil during vessel remodeling;
- Limited elongation-to-break, which defines the expansion range of scaffold

The authors concluded that recent large trials evaluating clinical results of BRS raised concerns about the safety and efficacy of these devices. Intensive research in the field is being conducted, stimulating the development of the next-generation BRS and the improvement of implantation techniques. As researchers observed a huge leap from 1st- to 2nd-generation drug-eluting metallic stents, the upcoming generation of BRS with thinner struts would be the most promising development to overcome the current limitations.
Kalra and associates (2017) stated that DES are the mainstay in the treatment of CAD using PCI. Innovations developed to overcome the limitations of prior generations of stents include BP stents, DES without a polymer, and bioabsorbable scaffolds. These investigators discussed the clinical profiles of 1st- and 2nd-generation coronary stents, and provided an up-to-date overview of design, technology, and clinical safety and efficacy profiles of newer generation coronary stents discussing the relevant clinical trials in this rapidly evolving area of interventional cardiology. These researchers noted that DES have previously been shown to be superior to BMS; 2nd-generation EES have proven to have superior outcomes compared with 1st-generation paclitaxel- and sirolimus-eluting stents, and the 2nd-generation zotarolimus-eluting stents appeared to be similar to the EES, though with a lesser degree of evidence. Stents with biodegradable polymers have not been shown to be superior to EES. Bioabsorbable scaffolds have not demonstrated better outcomes than current standard treatment with 2nd-generation DES; but have showed a concerning signal of late and very late ST; EES have the most favorable outcomes in terms of safety as well as efficacy in patients undergoing PCI. The authors concluded that newer innovations such as biodegradable polymers and bioabsorbable scaffolds lack clinical data to replace 2nd-generation DES as standard of care.

Lee and colleagues (2018a) noted that durable polymers used in DES are considered a potential cause of hypersensitivity inflammatory response adversely affecting stent healing. Using a sequential follow-up with optical coherence tomography (OCT), these investigators compared the differences in healing profiles of 2 DES with a biodegradable or durable polymer. A total of 60 patients with multi-vessel disease were prospectively enrolled to receive both study stents, which were randomly assigned to 2 individual vessels, a Resolute Integrity zotarolimus-eluting stent with a durable BioLinx polymer and a BioMatrix NeoFlex Biolimus A9-eluting stent with a biodegradable polylactic acid polymer; OCT was performed at baseline, then in 5 randomly assigned monthly groups at 2 to 6 months, and at 9 months in all patients. The primary end-point was the difference in OCT strut coverage at 9 months. Key secondary end-points included angiographic late lumen loss and composite MACE (cardiac death, MI, TLR, and definite or probable ST) at 9 months. Resolute Integrity zotarolimus-eluting stent showed significantly better strut coverage than BioMatrix NeoFlex Biolimus A9-eluting stent at 2 to 6 months (p < 0.001) and less variance of percent coverage at 9 months, 99.7 % (IQR, 99.1 to 100) versus 99.6 % (IQR, 96.8 to 99.9; difference, 0.10; 95 % CI: 0.00 to 1.05; p < 0.001). No significant difference was observed in MACE or angiographic end-points. The authors concluded that despite having a durable polymer, Resolute Integrity zotarolimus-eluting stent exhibited better strut coverage than BioMatrix NeoFlex Biolimus A9-eluting stent having a biodegradable polymer; both showed similar anti-proliferative efficacy. Moreover, this novel, longitudinal, sequential OCT protocol using each patient as own control could achieve conclusive results in small sample size.
van der Heijden and co-workers (2018) described the rationale and design of the randomized TWENTE IV multi-center trial (the BIONYX trial). This non-inferiority trial was designed to compare the safety and efficacy of 2 contemporary DESs -- a novel, durable polymer-coated stent versus an established bioabsorbable polymer-coated stent. The BIONYX trial is an investigator-initiated, prospective, randomized, patient- and assessor-blinded, international, multi-center study in all-comer patients with all types of clinical syndromes and lesions who require PCIs with DES. Patients at 7 study sites in the Netherlands, Belgium, and Israel were randomly assigned (1:1, stratified for gender and diabetes mellitus) to treatment with the novel, zotarolimus-eluting, durable polymer-coated Resolute Onyx stent that has a radiopaque, thin-strut, CoreWire stent platform versus the sirolimus-eluting, bioresorbable polymer-coated Orsiro stent (reference device) that has a very thin-strut, cobalt-chromium stent backbone. The primary end-point is the 1-year incidence of the composite clinical end-point target vessel failure (TVF) consisting of cardiac death, target vessel-related MI, or clinically indicated TVR. A power calculation, assuming a TVF rate of 6.0 % (non-inferiority margin 2.5 %), revealed that 2,470 study patients would give the study 80 % power (α level 5 %), allowing for up to 3 % loss to follow-up. The first patient was enrolled on October 7, 2015; on December 23, 2016, the last patient entered the study. The authors concluded that the BIONYX is a large-scale, prospective, randomized, international, multi-center trial comparing a novel DES with durable coating versus a reference DES with biodegradable coating in all-comers. The study is the first randomized assessment of the Resolute Onyx stent, which is an often-used DES outside the United States. They stated that this study will provide new insights into the clinical outcome of PCI with modern bioresorbable polymer versus permanent polymer DES in patients who reflect routine clinical practice. In addition, the study is the first randomized assessment of the Resolute Onyx stent, which is an often-used DES outside the United States.

Zhao and co-workers (2018) stated that the safety and efficacy of BP-DES compared to 2nd-generation DP-DES remain unclear in the real-world setting. These researchers compared the clinical outcomes of BP-DES with 2nd-generation DP-DES in an all-comer PCI registry. The study included a cohort of 1,065 patients treated with either BP-DES or DP-DES from January 2009 through October 2015. Propensity score matching was performed to account for potential confounders and produced 497 matched pairs of patients. The primary end-point was TLF at 1-year follow-up. The rates of TLF were comparable between BP-DES and DP-DES (8.7 % versus 9.1 %, p = 0.823) at 1 year. The rates of ST at 30 days (0.4 % versus 0.4 %, p = 1.00) and 1 year (0.8 % versus 0.8 %, p = 1.00) did not differ between BP-DES and DP-DES. There were no significant differences in other clinical outcomes including TVF (8.9 % versus 9.5 %, p = 0.741), ISR (1.8 % versus 1.0 %, p = 0.282), and cardiac death (6.4 % versus 7.4 %, p = 0.533) at 1 year. Multi-variate cox regression analysis showed that the risk of TLF at 1-year did not differ significantly between BP-DES and DP-DES (HR 0.94, p = 0.763). The authors concluded that the safety and efficacy of BP-DES were not better than DP-DES at 1-year follow-up.
Magnetically Coated Bioabsorbable Stents

Lee and colleagues (2018b) stated that the insertion of a stent in diseased arteries is a common endovascular procedure that can be compromised by the development of short- and long-term inflammatory responses leading to re-stenosis and thrombosis, respectively. While treatment with drugs, either systemic or localized, has decreased the incidence of re-stenosis and thrombosis these complications persist and are associated with a high mortality in those that present with ST. These investigators reasoned that if stents could be made to undergo accelerated endothelialization in the deployed region, then such an approach would further decrease the occurrence of ST and re-stenosis thereby improving clinical outcomes. Toward that objective, the 1st step necessitated efficient capture of progenitor stem cells, which eventually would become the new endothelium. To achieve this objective, these researchers engineered intrinsic ferro-magnetism within non-magnetizable, biodegradable magnesium (Mg) BMS; Mg stents were coated with biodegradable polylactide (PLA) polymer embedding magnetizable iron-platinum (FePt) alloy nano-particles, nano-magnetic particles, nMags, which increased the surface area and hence magnetization of the stent. nMags uniformly distributed on stents enabled capture, under flow, up to 50 ml/min, of systemically injected iron-oxide-labeled (IO-labeled) progenitor stem cells. Critical parameters enhancing capture efficiency were optimized, and these investigators demonstrated the generality of the approach by showing that nMag-coated stents can capture different cell types. The authors concluded that their work is a potential paradigm shift in engineering stents because implants are rendered as tissue in the body, and this "natural stealthiness" reduces or eliminates issues associated with pro-inflammatory immune responses post-implantation.

Polymer-Free Drug-Eluting Stents

Navarese et al (2014) stated that the safety and effectiveness of polymer-free DESs in clinical practice is currently subject of debate; RCTs conducted so far provided conflicting results or were under-powered to definitively address this question. These investigators examined the safety and effectiveness profile of polymer-free versus DP-DES by a comprehensive meta-analysis of RCTs. MEDLINE, Google Scholar, EMBASE and Cochrane databases were searched for RCTs comparing polymer-free to DP-DES. Safety end-points at short-term (less than or equal to 1 year) and long-term follow-up (greater than 1 year) were: death, MI and stent thrombosis (ST); main effectiveness end-points were: TLR and TVR. A total of 8 RCTs including 6,178 patients were included. No significant differences in mortality were observed between polymer-free and DP-DESs at both short- and long-follow up (OR [95 % CI]: 0.79 [0.58 to 1.08], p = 0.14; and 0.80 [0.58 to 1.10], p = 0.17 respectively); polymer free and DP-DESs provided comparable short and long-term MI rates; at short-term: OR [95 % CI]: 1.13 [0.83 to 1.54], p = 0.44 and at long-term: OR [95 % CI]: 1.27 [0.87 to 1.85], p = 0.22. Similarly, these 2 different devices proved equally effective
in regards to ST, TLR and TVR over the short and long follow-up period. The authors concluded that polymer-free DESs are as safe and effective as DP-DES; however, there is no evidence of any additional benefits provided by this new technology.

Antibody-Coated Stents

Antibody coated stents are proposed to accelerate vessel healing, prevent thrombi and minimize restenosis. They purportedly eliminate the need for prolonged antiplatelet therapy post-implantation. Currently, antibody coated stents are not FDA approved.

An UpToDate review on "Coronary artery stent types in development" (Cutlip and Abbott, 2014) states that "A number of drug eluting stent models, including abciximab-coated, beta-estradiol, and dexamethasone stents, have been tested and not carried forward into regulatory approval clinical trials in the United States. The Combo stent combines sirolimus elution from an abluminal biodegradable polymer matrix with a CD34 antibody layer. The CD34 antibody is directed toward circulating endothelial progenitor cells with a goal of increasing the rate of cellular coverage and thus decreasing the rate of stent thrombosis. In the first-in-man trial, the Combo stent was noninferior to a paclitaxel-eluting stent for outcomes of nine-month angiographic in-stent late lumen loss and 12-month major adverse cardiovascular events".

Drug-Eluting Stents for the Treatment of Intra-Coronary Stent Re-Stenosis

In a meta-analysis, Bajraktari and associates (2016) evaluated the safety and effectiveness of DEB compared with DES in patients with DES-ISR. These investigators carried out a systematic search and all randomized and observational studies that compared DEB with DES in patients with DES-ISR were included. The primary outcome measure- MACE-as well as individual events as TLR, ST, MI, CD and all-cause mortality, were analyzed. A total of 3 randomized and 4 observational studies were included (n = 2,052 patients); MACE (RR = 1.00, 95 % CI: 0.68 to 1.46, p = 0.99), TLR (RR = 1.15 [CI: 0.79 to 1.68], p = 0.44), ST (RR = 0.37 [0.10 to 1.34], p = 0.13), MI (RR = 0.97 [0.49 to 1.91], p = 0.93) and CD (RR = 0.73 [0.22 to 2.45], p = 0.61) were not different between patients treated with DEB and with DES. However, all-cause mortality was lower in patients treated with DEB (RR = 0.45 [0.23 to 0.87, p = 0.019) and in particular when compared to only 1st generation DES (RR 0.33 [0.15 to 0.74], p = 0.007). There was no statistical evidence for publication bias. The authors concluded that the findings of this meta-analysis showed that DEB and DES had similar safety and effectiveness for the treatment of DES-ISR.

Goel and co-workers (2016) performed a meta-analysis of observational and randomized studies to compare the outcomes of management of DES-ISR using DES, DEB, or balloon angioplasty (BA). Eligible studies (25 single-arm and 13 comparative, including 4 randomized studies with a total of 7,474 patients with DES-ISR) were identified using

Medline search and proceedings of international meetings. Outcomes studied included MACE, TLR, TVR, MI, ST, and mortality. Follow-up ranged from 0.5 to 3.5 years (mean of 1.4 years). The rate of TLR was significantly lower in the DES (OR 0.50, 95% CI: 0.36 to 0.69) and DEB (OR 0.31, 95% CI: 0.18 to 0.55) groups compared to BA. Similarly, TVR rate was significantly lower in the DES (OR 0.55, 95% CI: 0.39 to 0.77) and DEB (OR 0.32, 95% CI: 0.18 to 0.58) groups compared to BA. All other outcomes were similar between the DES/BA and DEB/BA comparisons; TLR was significantly lower in the DES group compared to BA for vessels less than or greater than 2.75 mm. The authors concluded that treatment of coronary DES-ISR with DES or DEB was associated with a reduction in the risk of TLR and TVR compared to BA alone. The relative risk reduction for TLR with DES was similar to DEB. They noted that DEBs have a potential role in the treatment of DES-ISR by avoiding placement of another layer of stent.

In a meta-analysis, Wang and colleagues (2017a) examined the effectiveness of DEB with DES in patients with ISR. Electronic databases were searched for RCTs and observational cohort studies that reported the clinical outcomes of using DEB comparing with DES implantation in patients with ISR. Clinical end-points such as MACE, MI, and CD were assessed. A total of 5 RCTs and 5 observational cohort studies with 962 patients in the DEB group and 908 patients in the DES group met inclusion criteria. There was no significant difference between DEB and DES in major clinical outcomes, such as MACE (OR 1.01; 95% CI: 0.64 to 1.58; p = 0.97; I² = 0%), all-cause death (OR 1.04; 95% CI: 0.54 to 1.98; p = 0.91; I² = 0%), CD (OR 1.44; 95% CI: 0.57 to 3.65; p = 0.44; I² = 0%), ST (OR 0.61; 95% CI: 0.16 to 2.33; p = 0.47; I² = 0%), and MI (OR 1.02; 95% CI: 0.53 to 1.94; p = 0.96; I² = 0%); DEB was associated with a significant increase in TLR (OR 1.54; 95% CI: 1.10 to 2.15; p = 0.01; I² = 57%). The authors concluded that treatment of ISR using DEB led to comparable clinical outcomes with DES implantation.

Furthermore, an UpToDate review on "Intracoronary stent restenosis" (Levin and Cutlip, 2017) states that "Placement of a newer generation drug-eluting stent (DES), and in particular an everolimus-eluting stent, is the preferred treatment for patients with ISR, irrespective of whether the original stent was bare metal or drug-eluting. The various potential percutaneous coronary interventional (PCI) techniques of plain old balloon angioplasty, bare metal stenting, or older generation stenting, newer generation stenting, atherectomy, brachytherapy, and DEBs, have been compared in multiple studies … The 2014 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guideline on myocardial revascularization recommends either drug-eluting stent (DES) or drug-coated balloons for the treatment of intracoronary stent restenosis (ISR) (bare metal stents [BMS] or DES)".

**Drug-Eluting and Non-Drug-Eluting Stents in Lower Extremity Peripheral Arterial Disease**
Kibrik and colleagues (2019) stated that DES have been promoted as an alternative to the traditional non-DES (nDES), and offer the potential for improved patency rates. However, DES are more expensive than nDES, and results comparing these stents outside of clinical trials have been limited. These investigators performed a retrospective review on all in-patient infra-inguinal lower extremity endovascular procedures between January 2014 and September 2016, which involved stent implantation. Procedures involving the common femoral artery, superficial femoral artery, and above knee popliteal artery were included. Procedures involving iliac, below knee popliteal, tibial, peroneal, and pedal arteries were excluded. The type of stent, number of stents, length of each stent, and location of stent were recorded for each procedure. Data on each patient’s Trans-Atlantic Inter Society Consensus II class were collected. End-points included stent thrombosis, re-stenosis, re-intervention, and limb loss. Post-operative arterial duplexes were obtained every 3 months to determine stent patency during follow-up visits. In-stent stenosis was defined as greater than 60 % narrowing on arterial duplex. Thrombosis was defined as in-stent occlusion, and limb loss involved only major amputations in the treated extremity. Bi-variate analysis and Students 2-sample t-test were used to analyze the data; IBM-SPSS - 22 was used for all analyses. A total of 212 patients underwent a total of 252 procedures during the study period. Of this group, 191 procedures met inclusion criteria. There were 21 lesions that were treated with both nDES and DES and they were excluded from further analysis. The average patient age was 73.2 ± 11.6 years; 68.6 % had hypertension, and 58.1 % had diabetes. Mean follow-up was 7.18 ± 7.96 months. The most common indication for intervention was claudication (53 %), followed by critical limb threatening ischemia (47 %); 124 procedures involved only nDES (Lifestent) (Bard, Tempe, AZ), 46 procedures involved only DES (Zilver) (Cook, Bloomington, IN). Comparison of nDES and DES showed the overall rate of thrombosis (11.1 % versus 16.7 %, p = 0.81), overall rates of re-stenosis (48.2 % versus 46 %, p = 1.0), re-intervention (13.7 % versus 14.3 %, p = 1.0), and limb loss (9.7 % versus 0.0 %, p = 0.38) was equivalent between the groups. The 6-month primary patency rate for nDES and DES (41.9 % versus 40.0 %, p = 1.0) was also equivalent. On average, the average lengths of nDES were longer than DES (19.2 ± 14.3 cm versus11.4 ± 5.7 cm) (p < 0.0001). DES results showed overall rates of 33 % re-stenosis, 7.1 % thrombosis, and no limb loss. There were no statistical differences between the nDES or DES groups with respect to gender, age, laterality, diabetes mellitus, coronary artery disease, gangrene, ulcers, hyperlipidemia, atrial fibrillation, deep vein thrombosis, claudication, critical limb-threatening ischemia, ipsilateral bypass, re-stenosis, thrombosis, limb loss, or ipsilateral amputation. Bi-variate analysis showed a higher incidence of hypertension for nDES patients (p = 0.001). There was no statistical difference between Trans-Atlantic Inter Society Consensus II classes and type of stent used (p = 0.95). The authors concluded that In this retrospective analysis from 1 institution, the use of an nDES or DES did not result in a statistically significant difference in the rate of thrombosis, re-stenosis, ipsilateral re-intervention, or ipsilateral amputation over a 2-year period when involving the CFA, SFA, and above knee popliteal artery.
Drug-Eluting Stents for the Treatment of Intra-Cranial Atherosclerotic Disease

Ye and colleagues (2019) noted that DES is a potential endovascular treatment for patients with symptomatic intra-cranial atherosclerotic disease (sICAD). However, evidence regarding the treatment of ICAD with DES is lacking. These investigators searched PubMed, Embase, Cochrane database (before December 21, 2017) for literature reporting the application of DES in the treatment of sICAD. The main outcomes were as follows: the incidence of any stroke or death within 30 days (peri-operative complications), ischemic stroke in the territory of the qualifying artery beyond 30 days (long-term complications), ISR and symptomatic ISR during follow-up. Those studies with mean stenosis rate greater than 70% and less than 70% were defined as severe and moderate stenosis group, respectively. The random effect model was used to pool the data. Of 518 articles, 13 studies were eligible and included in this analysis (n = 336 patients with 364 lesions). After the implantation of DES, peri-operative complications (mortality = 0) occurred in 6.0% (95% CI: 2.0% to 11.9%), long-term complications occurred in 2.2% (95% CI: 0.7% to 4.5%), ISR rate was 4.1% (95% CI: 1.6% to 7.7%) and the symptomatic ISR rate was only 0.5% (95% CI: 0 to 2.2%). In addition, subgroup analysis showed that the peri-operative complication rate in severe stenosis group [10.6% (95% CI: 6.5% to 15.7%)] was significantly (p < 0.01) higher than that in moderate stenosis group [1.0% (95% CI: 0.3% to 3.5%)]. The authors concluded that endovascular DES implantation was a relatively safe and effective method compared with stents or medical management group in SAMMPRIS and VISSIT trials. However, a higher pre-operative stenosis rate may imply a higher risk of peri-operative complications. These researchers stated that further studies are needed.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>Other CPT codes related to the CPB:</td>
<td></td>
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<tr>
<td>0075T - 0076T</td>
<td>Transcatheter placement of extracranial vertebral artery stent(s), including radiologic supervision and interpretation, open or percutaneous</td>
</tr>
<tr>
<td>+0205T</td>
<td>Intravascular catheter-based coronary vessel or graft spectroscopy (eg, infrared) during diagnostic evaluation and/or therapeutic intervention including imaging supervision, interpretation, and report, each vessel (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>+0291T</td>
<td>Intravascular optical coherence tomography (coronary native vessel or graft) during diagnostic evaluation and/or therapeutic intervention, including imaging supervision, interpretation, and report; initial vessel (List separately in addition to primary procedure)</td>
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<td>Code</td>
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<tr>
<td>37236 - 37237</td>
<td>Transcatheter placement of an intravascular stent(s) (except lower extremity artery(s) for occlusive disease, cervical carotid, extracranial vertebral or intrathoracic carotid, intracranial, or coronary), open or percutaneous, including radiological supervision and interpretation and including all angioplasty within the same vessel, when performed</td>
</tr>
<tr>
<td>37238 - 37239</td>
<td>Transcatheter placement of an intravascular stent(s), open or percutaneous, including radiological supervision and interpretation and including angioplasty within the same vessel, when performed</td>
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<tr>
<td>61635</td>
<td>Transcatheter placement of intravascular stent(s), intracranial (e.g., atherosclerotic stenosis), including balloon angioplasty, if performed</td>
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<tr>
<td>92928 - 92929</td>
<td>Percutaneous transcatheter placement of intracoronary stent(s), with coronary angioplasty when performed</td>
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<tr>
<td>92933 - 92934</td>
<td>Percutaneous transluminal coronary atherectomy, with intracoronary stent, with coronary angioplasty when performed</td>
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<tr>
<td>92937 - 92938</td>
<td>Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of intracoronary stent, atherectomy and angioplasty, including distal protection when performed</td>
</tr>
<tr>
<td>92941</td>
<td>Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel</td>
</tr>
<tr>
<td>92943 - 92944</td>
<td>Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of intracoronary stent, atherectomy and angioplasty</td>
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HCPCS codes covered if selection criteria are met:

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<th>Description</th>
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<td>C1874</td>
<td>Stent, coated / covered, with delivery system [covered for (FDA)-approved everolimus, paclitaxel, sirolimus, and zotarolimus eluting stents only] [not covered for biodegradable (biodegradable, biodegradable) polymer drug eluting stents] [not covered for antibody-coated coronary stents] [not covered for magnetically-coated bioabsorbable stents]</td>
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<tr>
<td>C1875</td>
<td>Stent, coated / covered, without delivery system [covered for (FDA)-approved everolimus, paclitaxel, sirolimus, and zotarolimus eluting stents only] [not covered for biodegradable (biodegradable, biodegradable) polymer drug eluting stents] [not covered for antibody-coated coronary stents] [not covered for magnetically-coated bioabsorbable stents]</td>
</tr>
</tbody>
</table>

Other HCPCS codes related to the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9600 - C9601</td>
<td>Percutaneous transcathe ter placement of drug eluting intracoronary stent(s), with coronary angioplasty when performed</td>
</tr>
<tr>
<td>C9602 - C9603</td>
<td>Percutaneous transluminal coronary atherectomy, with drug eluting intracoronary stent, with coronary angioplasty when performed</td>
</tr>
<tr>
<td>C9604 - C9605</td>
<td>Percutaneous transluminal revascularization of or through coronary artery bypass graft (internal mammary, free arterial, venous), any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including distal protection when performed</td>
</tr>
<tr>
<td>C9606</td>
<td>Percutaneous transluminal revascularization of acute total/subtotal occlusion during acute myocardial infarction, coronary artery or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty, including aspiration thrombectomy when performed, single vessel</td>
</tr>
<tr>
<td>C9607</td>
<td>Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty; single vessel</td>
</tr>
<tr>
<td>C9608</td>
<td>Percutaneous transluminal revascularization of chronic total occlusion, coronary artery, coronary artery branch, or coronary artery bypass graft, any combination of drug-eluting intracoronary stent, atherectomy and angioplasty; each additional coronary artery, coronary artery branch, or bypass graft (list separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

ICD-10 codes covered if selection criteria are met:

- I20.1 - I20.9: Angina pectoris
- I25.10 - I25.9: Atherosclerotic heart disease of native coronary artery
- T82.01xA - T82.9xxS: Complications of cardiac and vascular prosthetic devices, implants and grafts [intra-coronary stent re-stenosis]

ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):

- I20.0: Unstable angina
- I65.01 - I65.09: Occlusion and stenosis of vertebral artery
- I65.21 - I65.29: Occlusion and stenosis of carotid artery
- I67.2: Cerebral atherosclerosis
- I70.1 - I70.92: Atherosclerosis of renal artery and extremities
- I77.1: Stricture of artery
- K22.2: Esophageal obstruction
- K31.1: Adult hypertrophic pyloric stenosis
- K80.00 - K87: Disorders of gallbladder, biliary tract and pancreas
- M31.4: Aortic arch syndrome [Takayasu]
<table>
<thead>
<tr>
<th>Code</th>
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</tr>
</thead>
<tbody>
<tr>
<td>N18.1 - N18.9</td>
<td>Chronic kidney disease (CKD) [multi-vessel disease]</td>
</tr>
<tr>
<td>Q40.0</td>
<td>Congenital hypertrophic pyloric stenosis</td>
</tr>
<tr>
<td>R13.10 - R13.19</td>
<td>Dysphagia</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


111. Nakagawa Y. Which should be indicated for patients with ACS, DES or BMS? Nippon Rinsho. 2011;69(2):271-274.


122. Beathard GA. Use of stents for venous stenosis associated with dialysis vascular access. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed May 2013.


132. Cutlip D, Abbott JD. Coronary artery stent types in development. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed April, 2014.


179. Fairman RM. Carotid artery stenting and its complications. UpToDate [online serial]. Waltham, MA: UpToDate; Reviewed February 2018.

181. Morasch MD. Vertebral artery revascularization. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2017.


185. Baron TH, Law R. Use of expandable stents in the esophagus. UpToDate [online serial]. Waltham, MA; UpToDate; reviewed December 2017.


Amendment to
Aetna Clinical Policy Bulletin Number: 0621 Drug-Eluting Stents

There are no amendments for Medicaid.