Safety and Efficacy of Drug-Eluting Stents Compared With Bare Metal Stents in ST-Elevation Myocardial Infarction

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Drug-eluting stents (DES) reduce restenosis and the need for repeat revascularization, but patients with ST-segment elevation myocardial infarction (STEMI) were excluded from many of the trials that established the safety and efficacy of DES. Because of the unstable nature of lesions associated with STEMI, these patients are considered high risk, and often experience higher rates of adverse events. There is concern that DES may increase the risk of stent thrombosis, particularly late and very late stent thrombosis, in STEMI patients. Evidence also suggests that although DES reduce target vessel revascularization, this benefit may be lost after extended follow-up due to procedures necessitated by increased stent thrombosis. Several randomized trials, meta-analyses, and registry studies have been conducted to compare DES with bare metal stents in patients with STEMI, but many of the studies are not large scale and the length of follow-up has been limited in duration. This review summarizes the data comparing DES with bare metal stents in patients with STEMI.
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Key words: Bare metal stent • Drug-eluting stent • Percutaneous coronary intervention • ST-segment elevation myocardial infarction

Percutaneous coronary intervention (PCI) is considered the treatment of choice for patients presenting with acute myocardial infarction (MI), as it improves clinical outcome and reduces the risk of recurrent ischemia and death to a greater degree than thrombolytic therapy.[1] Stent placement improves outcomes more favorably than balloon angioplasty alone by decreasing the rates of restenosis and target vessel revascularization (TVR), and may also reduce mortality in high-risk patients.[2,3] Drug-eluting stents (DES) further decrease the

incidence of restenosis and have been found to be safe for most presenting situations, as they do not significantly increase the risk of stent thrombosis, death, or recurrent MI when compared with bare metal stents (BMS).[4-7] DES implantation decreases the rates of death and recurrent MI compared with BMS.[8] The safety and efficacy of DES have been confirmed in long-term studies, with a sustained reduction in TVR beyond 1-year follow-up and similar rates of death and recurrent MI compared with BMS.[9] However, the original clinical trials that resulted in the US Food and Drug Administration approval of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) excluded patients with complex lesions or recent MI, so DES use for these patients is considered off label.[10,11]

DES implantation decreases the rates of death and recurrent MI compared with BMS.

High-risk patients, such as those experiencing ST-elevation myocardial infarction (STEMI) and other acute coronary syndromes, have demonstrated higher rates of stent thrombosis when treated with DES.[12] Because many cases of STEMI are caused by ruptured plaques, DES are thought to increase exposure to the lipid-rich necrotic core of the lesion. This environment is rich in thrombotic and inflammatory factors that enhance platelet activation.[13] In addition, stents treated with lipophilic drugs such as paclitaxel and sirolimus may inhibit vascular healing by decreasing endothelialization and smooth muscle cell proliferation.[14]

Several studies have investigated the potential increase in stent thrombosis associated with the implantation of DES in patients with STEMI. Daemen and colleagues[15] conducted a long-term observational study, the results of which suggest that the use of DES may increase the incidence of stent thrombosis after 3 years of follow-up, at which point the beneficial reduction of TVR is lost due to the additional procedures required to treat the stent thromboses. A meta-analysis demonstrated the effectiveness of DES at reducing TVR in STEMI patients, but the relatively short follow-up periods for all of the included trials (1-2 years) were not of sufficient duration to demonstrate the relative safety of DES compared with BMS.[16] Reaching a conclusion about the safety and efficacy of DES in the treatment of STEMI requires long-term follow-up and large patient cohorts that have sufficient power to delineate statistically significant differences in safety endpoints.

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Recently, large-scale trials and registry studies have been conducted that may give new perspective in this controversial debate.

Stent Thrombosis

Stent thrombosis is one of the major risks associated with DES implantation in patients with STEMI. The Academic Research Consortium defines several distinct categories of stent thrombosis based on the evidence available to confirm its presence, describing stent thrombosis as definite, probable, or possible.[17] A classification of definite stent thrombosis requires angiographic or pathologic (obtained at autopsy) confirmation of thrombotic occlusion, whereas probable stent thrombosis is characterized by unexplained death within 30 days of the procedure, or an MI due to ischemia in the region supplied by the stented vessel with no other obvious cause. Possible stent thrombosis is suspected when an unexplained death occurs in the period 30 days following stent implantation until the end of study follow-up. Stent thromboses are also divided into classes based on the time of onset, with acute stent thrombosis occurring within 24 hours after stent placement, subacute stent thrombosis occurring within 30 days after stent placement, late stent thrombosis occurring from 1 month to 1 year after stent placement, and very late stent thrombosis occurring after 1 year.

Stent thrombosis is one of the major risks associated with DES implantation in patients with STEMI.

Stent thrombosis results in altered blood flow through the occluded artery. The degree of occlusion caused by stent thrombosis determines its grade within the Thrombolysis in Myocardial Infarction (TIMI) system. Grade 0 signifies a complete lack of perfusion beyond the occlusion. Grade 1 describes a lesion in which the contrast material passes through the occlusion but fails to perfuse the vessel bed. Grade 2

occlusions allow partial perfusion, and grade 3 lesions show full perfusion equivalent to that of an uninvolved section of the same vessel.[18] A successful stent implantation is described as achieving TIMI grade 3.

Several predictors for thrombotic events have been identified, such as renal failure, low ejection fraction, bifurcation lesions, stent length, procedures for acute MI, and diabetes, with the most important predictor shown to be premature discontinuation of antiplatelet therapy such as clopidogrel.[19,20] Incomplete stent apposition is also associated with an increased risk of stent thrombosis following DES implantation.[21] The guidelines released by the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions recommend that dual antiplatelet therapy be continued for at least 12 months after DES implantation.[22] However, many older randomized trials and observational studies discontinued antiplatelet therapy after as little as 3 months, which may increase the risk of stent thrombosis, particularly in patients treated with DES. The increased risk of stent thrombosis seen with DES versus BMS in some observational studies appears to be entirely composed of late and very late stent thrombosis, as rates of thrombosis begin to differ at 6 months after stent implantation, coinciding with the cessation of clopidogrel treatment, and continue to the end of the 3-year follow-up.[23] A meta-analysis by Stone and associates[24] observed that the difference in stent thrombosis rates between DES and BMS was only significant if analyzed for the period of 1 to 4 years after the procedure, signifying very late stent thromboses.

Safety and Efficacy Outcomes of DES in Patients With STEMI

Randomized, Controlled Trials

A number of small- to moderate-scale trials have been conducted to determine whether DES are superior to BMS in the treatment of STEMI (Tables 1 and 2). Collectively, the results from these small- to moderate-scale randomized trials support the assertion that DES reduce rates of TVR and binary restenosis without significantly impacting safety endpoints such as recurrent MI and death. Some results even suggest that DES may improve safety by reducing the rate of major adverse cardiac events (MACE). The STRATEGY (High-Dose Bolus Tirofiban and

Table 1
Main Characteristics of Randomized Clinical Trials of STEMI Patients

Study	Stent Type	DES/BMS (N)	Follow-Up (mo)	Antiplatelet Duration, DES (mo)
DEDICATION[32]	PES and SES	313/313	8	12
Diaz de la Llera LS et al.[27]	SES	60/54	12	9
HAAMU-STENT[28]	PES	82/82	12	12
HORIZONS-AMI[35]	PES	2257/749	12	6-12
MISSION![29]	SES	158/152	12	12
MULTISTRATEGY[34]	SES	372/372	8	3
PASEO[37]	PES and SES	180/90	12, 24	6
PASSION[26]	PES	310/309	12	6
SELECTION[36]	PES	39/37	7	9
SESAMI[30]	SES	154/153	12	12
STRATEGY[25]	SES	87/88	8	3
TYPHOON[33]	SES	355/357	12	6

BMS, bare metal stent; DEDICATION, Drug Elution and Distal Protection in Acute Myocardial Infarction; DES, drug-eluting stent; HAAMU-STENT, Helsinki Area Acute Myocardial Infarction Treatment Reevaluation; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MISSION!, A Prospective Randomised Controlled Trial to Evaluate the Efficacy and Safety of Drug-Eluting Stents Versus Bare-Metal Stents for the Treatment of Acute Myocardial Infarction; MULTISTRATEGY, Multicentre Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study; PASEO, Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty; PASSION, Paclitaxel-Eluting Versus Uncoated Stents in Primary Percutaneous Coronary Intervention; PES, paclitaxel-eluting stent; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Versus Conventional Stent in Acute Myocardial Infarction; SES, sirolimus-eluting stent; SESAMI, Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction; STEMI, ST-elevation myocardial infarction; STRATEGY, High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare Metal Stent in Acute Myocardial Infarction; TYPHOON, Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty.

Table 2
Randomized Clinical Trials Data

	Stent Thrombosis (%)			TVR (%)			Death (%)			Myocardial Infarction (%)			Safety Endpoint (%)		
Study Name	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**
DEDICATION[32]	–	–	–	5.1[a]	13.1[a]	< .001[a]	5.1	2.6	.14	1.6	2.6	.42	8.9	14.4	< .05
Diaz de la Llera LS et al.[27]	1.7[b]	0[b]	.341[b]	0	5.7	.064	5	3.6	.736	6.7	5.4	.26	6.7	11.1	.402
HAAMU-STENT[28]	2.4	6.1	NS	3.7	11	.072	9.8	4.9	.23	1.2	4.9	.37	13	17	.52
HORIZONS-AMI[35]	3.2	3.4	.77	5.8	8.7	.006	3.5	3.5	.98	3.7	4.5	.31	8.1	8	.92
MISSION![29]	1.3	2	.68	5.1	13.2	.01	1.3	2.6	.44	5.7	9.2	.24	7	15.1	.02
MULTISTRATEGY[34]	2.7	4	.31	3.2	10.2	< .001	3	4	.42	3.2	4.6	.34	7.8	14.5	.004
PASEO[37 c]	3.3	4.4	.7	4.4[a]	14.4[a]	.023[a]	4.4	6.7	.52	3.3	6.7	.3	11.1	24.4	.02
PASEO[37 d]	2.2	4.4	.41	3.3[a]	14.4[a]	.016[a]	3.3	6.7	.3	4.4	6.7	.45	11.1	24.4	.02
PASEO[37 e]	5.6	6.7	.74	5.6[a]	17.8[a]	.01[a]	6.7	10	.42	5.6	11.1	.17	16.7	32.2	.015
PASEO[37 f]	3.3	6.7	.31	4.4[a]	17.8[a]	.004[a]	5.6	20	.26	6.7	11.1	.26	15.6	32.2	.009
PASSION[26]	1	1	.99	5.3[a]	7.8[a]	.23[a]	4.6	6.5	.3	1.7	2	.74	8.8	12.8	.12
SELECTION[36]	0[b]	5[b]	.15[b]	17.5	42.5	.05	2.5	7.5	.61	0	2.5	.99	7.5	42.5	.001
SESAMI[30]	1.2	0.6	.43	5	13.1	.015	1.8	4.3	.36	1.8	1.8	.99	6.8	16.8	.005
STRATEGY[25]	0[b]	0[b]	.99[b]	7	20	.01	8	9	.78	7	9	.6	18	32	.04
TYPHOON[33]	2	3.4	.35	5.6	13.4	< .001	2.3	2.2	1	1.1	1.4	1	7.3	14.3	.004

BMS, bare metal stent; DEDICATION, Drug Elution and Distal Protection in Acute Myocardial Infarction; DES, drug-eluting stent; HAAMU-STENT, Helsinki Area Acute Myocardial Infarction Treatment Reevaluation; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; MISSION!, A Prospective Randomised Controlled Trial to Evaluate the Efficacy and Safety of Drug-Eluting Stents Versus Bare-Metal Stents for the Treatment of Acute Myocardial Infarction; MULTISTRATEGY, Multicentre Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study; NS, not significant; PASEO, Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty; PASSION, Paclitaxel-Eluting Versus Uncoated Stents in Primary Percutaneous Coronary Intervention; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Versus Conventional Stent in Acute Myocardial Infarction; SESAMI, Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction; STRATEGY, High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare Metal Stent in Acute Myocardial Infarction; TVR, target vessel revascularization; TYPHOON, Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty.
[a]The value given is target lesion revascularization, not TVR.
[b]The value given is late stent thrombosis only.
[c]Results from paclitaxel-eluting stent (PES) arm with 12-month follow-up.
[d]Results from sirolimus-eluting stent (SES) arm with 12-month follow-up.
[e]Results from PES arm with 24-month follow-up.
[f]Results from SES arm with 24-month follow-up.

Sirolimus-Eluting Stent Versus Abciximab and Bare Metal Stent in Acute Myocardial Infarction) trial[25] demonstrated that patients treated with SES had significantly lower rates of MACE (18% vs 32%; $P = .04$) and TVR (7% vs 20%; $P = .01$) compared with patients treated with BMS with no significant difference in the incidence of stent thrombosis at a follow-up of 8 months. MACE are typically defined as a composite of death, recurrent MI, and TVR.

Both the PASSION (Paclitaxel-Eluting Versus Uncoated Stents in Primary Percutaneous Coronary Intervention) trial[26] and a study by Diaz de la Llera and coworkers[27] failed to achieve statistical significance for any endpoint within a year of follow-up, including target lesion revascularization (TLR) (PASSION: 5.3% in DES vs 7.8% in BMS; $P = .23$) and TVR (Diaz de la Llera et al: 0% in DES vs 5.7% in BMS; $P = .064$). These studies' lack of power may be due to their choice of following up clinically instead of angiographically, as angiographic follow-up detects restenosis even in the

absence of ischemia, which potentially would have increased the TVR rates. However, the HAAMU-STENT (Helsinki Area Acute Myocardial Infarction Treatment Reevaluation) study[28] included angiographic follow-up and still did not achieve statistically significant differences between BMS and DES for any endpoint at 12-month follow-up, so that the lack of power in this case may have been due to the very small patient cohort. Though these results do not contribute much to the efficacy argument, they may support the hypothesis that DES do not significantly increase the risk of stent thrombosis or MACE. Both the MISSION! (A Prospective Randomised Controlled Trial to Evaluate the Efficacy and Safety of Drug-Eluting Stents Versus Bare-Metal Stents for the Treatment of Acute Myocardial Infarction)[29] and SESAMI (Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction)[30] trials demonstrated significant reduction in TVR and MACE with DES without any increase in the risk of stent thrombosis, death, or recurrent MI during their year-long follow-up. Despite these results that support the safety and efficacy of DES over BMS, the MISSION! trial included a secondary endpoint of late stent malapposition, which has been associated with an increased risk of very late stent thrombosis, and may be caused by remodeling of the vessel wall as an adverse effect of drug treatment from the stent.[31] There was a significant increase in late stent malapposition in the DES treatment group (25% vs 5.0% in BMS patients; $P < .001$) as detected by intravascular ultrasound. The SESAMI trial also demonstrated a benefit with DES for the secondary endpoint of target vessel failure (8.7% vs 18.7% for BMS; $P = .007$), defined as a composite of TVR, recurrent MI, and target vessel–related death within 12 months.[31] The small number of patients in each of these trials (< 350 patients total) limits the absolute conclusions that may be drawn, but results do not suggest an increased risk of adverse outcomes with DES compared with BMS.

The DEDICATION (Drug Elution and Distal Protection in Acute Myocardial Infarction),[32] TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty),[33] and MULTISTRATEGY (Multicentre Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study)[34] trials have provided further support for the TLR and MACE reduction associated with DES, as their slightly larger treatment groups (600-750 patients total) increase their statistical power. All 3 trials had favorable results, and demonstrated significant advantages with DES in terms of decreasing the rates of TVR ($P < .001$ for all). None of the individual safety endpoints (stent thrombosis, recurrent MI, and death) varied significantly among treatment groups, and the composite safety endpoint of MACE after 8 months of follow-up (DEDICATION and MULTISTRATEGY) or target vessel failure after 12 months of follow-up (TYPHOON) was lower in the DES treatment group ($P < .05$ for DEDICATION; $P < .004$ for TYPHOON and MULTISTRATEGY). Though the MULTISTRATEGY trial was also investigating the relative efficacy of tirofiban and abciximab, its 2×2 factorial design ensured proper control such that 2 treatment groups varied only in the choice of stent type, and results were not impacted by glycoprotein IIb/IIIa inhibitor choice.

The largest randomized trial, HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction),[35] produced findings that support the increased efficacy of PES at reducing TVR after 12 months of follow-up. However, there is no accompanying improvement in the composite safety endpoint (recurrent MI, death, stent thrombosis, and stroke) as had been demonstrated by many previous studies such as MULTISTRATEGY, DEDICATION, and TYPHOON, which may in part be attributed to a lower overall event rate due to the decision not to perform an angiographic follow-up. Decreasing the number of revascularization procedures by eliminating the oculostenotic reflex may have played a role in the loss of significant variation in safety outcomes among groups. The oculostenotic reflex is the tendency to treat any restenosis discovered during angiographic follow-up without taking into account the presence or absence of ischemia demonstrated symptomatically. This practice may have had an influence in several trials, such as the SELECTION (Single-Center Randomized Evaluation of Paclitaxel-Eluting Versus Conventional Stent in Acute Myocardial Infarction) trial,[36] which included angiographic follow-up after 7 months. The rates of TVR were lower with PES compared with BMS (17.5% vs 42.5%; $P = .05$), but the TVR rates observed in the BMS group are much higher than the results for any of the other trials included in this review. However, the SELECTION trial did demonstrate a significant reduction in MACE with DES (7.5% vs 42.5% for BMS; $P = .001$), unlike HORIZONS-AMI.

Similar to the HORIZONS-AMI trial, the PASEO (Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) trial[37] did not use routine angiographic follow-up to detect restenosis

necessitating TVR, so the significance achieved for the safety and efficacy of DES is unlikely to be overestimated. The PASEO trial compared patients treated with SES, PES, and BMS after 12 and 24 months of follow-up. Its findings reinforce those of previous trials, as both types of DES had lower TLR rates at both follow-up durations, supporting the greater long-term efficacy of DES over BMS. SES had slightly lower rates of TLR at both durations of follow-up, and were not associated with significant differences in MACE. There were no significant differences between treatment groups for any of the individual safety endpoints (death, reinfarction, TLR, and stent thrombosis), but the composite MACE endpoint of death, recurrent MI, and TLR was significantly reduced in both DES groups after 1 and 2 years of follow-up. Similar to both the HORIZONS-AMI and SELECTION trials, the length of clopidogrel therapy was also kept standard between DES and BMS treatment groups, reducing the possible impact of dual antiplatelet therapy on outcomes. However, these trials differed in the recommended duration of clopidogrel therapy, with PASEO requiring only 6 months, SELECTION requiring 9 months, and HORIZONS-AMI requiring 6 months but recommending 12 months of therapy.

Discontinuation of dual antiplatelet therapy has an observed association with an increase in stent thrombosis, so it is valuable for follow-up to extend significantly beyond the end of clopidogrel therapy. It has been proposed that the main risk associated with DES is late or very late stent thrombosis, which may not have been observed during the 12 months or less of follow-up in each of these studies. The BASKET-AMI (Basel Stent Kosten-Effektivitäts in Acute Myocardial Infarction) trial[38] followed patients for 3 years, and found that DES patients had a slightly higher rate of stent thrombosis compared with BMS patients, suggesting that further studies with follow-up periods of at least 2 to 3 years will be necessary to detect a significant increase in stent thrombosis. Larger patient populations would also improve the certainty with which conclusions may be drawn from study findings and provide the necessary power to make determinations about safety endpoints.

One potential confounding variable that could be present in randomized trials is the duration of dual antiplatelet therapy, especially the length of treatment with thienopyridines such as clopidogrel. Current guidelines differentiate between BMS and DES in the recommended duration of clopidogrel, as DES patients are advised to continue therapy for at least 12 months, whereas a minimum of 1 month is recommended for BMS patients. In the most recent update, clopidogrel is recommended for "ideally up to 12 months" even in BMS patients.[22] Many trials were conducted before these guidelines were published or chose not to adhere to their recommendations, and only required 3 to 9 months of clopidogrel treatment.[25-28,34,35,37] The incidence of stent thrombosis in STEMI patients treated with DES has been shown to increase with premature discontinuation of dual antiplatelet therapy based on the results of the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) registry.[39] In contrast, De Luca and colleagues[40] conducted a meta-regression analysis of several randomized trials that compared DES with BMS in patients with STEMI and reported that 1-year outcomes in STEMI patients receiving clopidogrel after PCI were not affected by the duration of dual antiplatelet therapy. However, these results should be interpreted carefully, as outcomes beyond 1 year were not considered, and individual patient data were not used in the analysis.

Discontinuation of dual antiplatelet therapy has an observed association with an increase in stent thrombosis . . .

Meta-Analyses

To increase the number of patients in each treatment group while still retaining the benefits and controls of randomized clinical trials, meta-analyses have been performed on a larger scale than would be possible for most randomized studies (Tables 3 and 4). Additionally, 2 meta-analyses included studies with follow-up extending to 24 or 36 months, allowing a comparison of short- and long-term results. Results were consistent among the meta-analyses reviewed, as all 5 found a significant reduction in TVR or TLR with DES ($P < .001$ for Brar SS et al.[43] and Kastrati A et al.[51]; $P < .0001$ for De Luca G et al.[16] [18- to 24-month follow-up], De Luca G et al.[44] [24- to 36-month follow-up], and Pasceri V et al.[41]; $P < .00001$ for De Luca G et al.[16] [12-month follow-up] and De Luca G et al.[44] [12-month follow-up]) without any increase in risk of stent thrombosis, death, recurrent MI, or MACE. The meta-analysis with the briefest duration of follow-up was that conducted by Pasceri and coauthors,[41] which only collected follow-up data for 8 to 12 months. The authors had analyzed extracted

Table 3
Main Characteristics of Meta-Analyses

Study	Stent Type	DES/BMS (N)	Follow-Up (mo)	Antiplatelet Duration, DES (mo)
Brar SS et al.[43]	PES and SES	4515/2837	7-18	3-12
De Luca G et al.[16]	PES and SES	1888/1719	12	3-12
De Luca G et al.[16]	PES and SES	654/524	18-24	3-12
De Luca G et al.[44]	PES and SES	1389/1380	12	3-12
De Luca G et al.[44]	PES and SES	284/285	24-36	3-12
Kastrati A et al.[51]	PES and SES	1474/1312	12-24	3-12
Pasceri V et al.[41]	PES and SES	1177/1180	8-12	3-12

BMS, bare metal stent; DES, drug-eluting stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent.

Table 4
Meta-Analyses Data

	Stent Thrombosis (%)			TVR (%)			Death (%)			Myocardial Infarction (%)			Safety Endpoint (%)		
Study	DES	BMS	*P* Value	DES	BMS	*P* Value	DES	BMS	*P* Value	DES	BMS	*P* Value	DES	BMS	*P* Value
Brar SS et al.[43]	2.8	2.6	.81	5.3	11.5	< .001	3.7	4.3	.36	3.4	3.8	.12	–	–	–
De Luca G et al.[16 a]	1.6	2.2	.27	5	12.6	< .00001	4.1	4.4	.59	3.1	3.4	.43	–	–	–
De Luca G et al.[16 b]	1.1	1.9	.23	6	13.5	< .0001	6.1	7.6	.07	4.7	4.4	.92	–	–	–
De Luca G et al.[44 a]	2.2	2.5	.6	4.5	12.7	< .00001	3	4.2	.08	3	4.3	.06	–	–	–
De Luca G et al.[44 c]	2.5	2.4	1	8.1	19.6	< .0001	6.3	9.5	.17	8.1	8.8	.77	–	–	–
Kastrati A et al.[51]	1.7	2.2	.43	0.05[d]	1.3[d]	< .001[d]	4.1	5.1	.14	3.1	4	.11	10.7	19.2	< .001
Pasceri V et al.[41]	2.3	2.6	.73	4.8[d]	12[d]	< .0001[d]	2.8	3.1	NS	5.8	6.9	NS	9.3	17.6	< .0001

BMS, bare metal stent; DES, drug-eluting stent; NS, not significant; TVR, target vessel revascularization.
[a]Results from 12-month follow-up.
[b]Results from 18- to 24-month follow-up.
[c]Results from 24- to 36-month follow-up.
[d]The value given is target lesion revascularization, not TVR.

information from summary data from meeting abstracts, which is less reliable than conducting an analysis based solely on individual patient data. Though this trial produced favorable results, its findings were called into question by Kastrati and associates[42] in their meta-analysis. The authors extracted information directly from patient data, and achieved similar favorable results in terms of the safety and efficacy of DES, including findings from a study with a 24-month follow-up period. Brar and colleagues[43] completed a meta-analysis that included data from 7352 patients, making it the largest study to date. The analysis of 13 randomized trials yielded results that favored DES over BMS, as TVR rates were significantly reduced and safety endpoints did not differ greatly. A separate meta-analysis of registry studies was also completed, and showed similar favorable results. They noted no difference in outcomes between studies requiring less than or more than 6 months of clopidogrel therapy after PCI, though current guidelines recommend a duration of 12 months.[22] However, this study was also conducted using data provided in study

publications rather than analyzing individual patient data, so its reliability may be questioned.

To determine whether there is a measurable risk of late stent thrombosis with DES, studies with longer follow-up periods are necessary. De Luca and associates[16,44] have completed 2 recent meta-analyses that compare outcomes between those reported at 1 year and 2 to 3 years of follow-up. The first of these meta-analyses included studies with follow-up at 12 months and at 18 to 24 months.[16] The outcomes for these 2 studies were very similar, and showed a significant reduction in TVR ($P < .0001$ at 18- to 24-month follow-up and $P < .00001$ at 12-month follow-up) with no associated increase in stent thrombosis, death, recurrent MI, or MACE. These results suggest that there is no significant increase in adverse events between 1 and 2 years after stent implantation, though extending follow-up to 3 to 5 years would provide greater assurance. De Luca and coauthors[44] then published a meta-analysis that compared a group of studies with 12 months of follow-up to a group with 24 to 36 months of follow-up, and again found very similar results between groups. Though TVR was significantly reduced in both DES groups (short- and long-term follow-up), the safety endpoints were not significantly different based on BMS or DES treatment. The findings from this meta-analysis support the assertion that the benefits of DES in reducing TVR may extend up to 3 years, and there was no evidence to support an increased risk of stent thrombosis after the first year of follow-up. However, the number of patients for which there are data at 2 to 3 years was much smaller than the group at 1 year. Larger study populations would allow greater certainty of the validity of these results.

Registry Studies

Given the limitations of randomized clinical trials, such as their exclusion of certain high-risk patient populations, registry studies have been undertaken to establish the "real-world" safety and efficacy of DES in patients with STEMI. By not excluding patients with more serious presentations, these studies produce findings that may be more applicable to patients seen in actual clinical practice. However, registry studies have their own set of limitations, such as publication bias, confounders, and the tendency to overestimate treatment effects. Overall, among the registry studies conducted on the use of DES in STEMI, none observed a significant increase in stent thrombosis and most demonstrated a significant reduction in TVR with DES compared with BMS. None of these studies observed an increased risk of recurrent MI or death, and many even demonstrated a significant reduction in MACE associated with the use of DES. Among the single-center registries with follow-up periods of 1 year or less, there is a consensus that there is no additional risk associated with the use of DES for individual safety endpoints, including stent thrombosis (Tables 5 and 6). These studies were conducted by Cheneau and colleagues,[45] Kupferwasser and colleagues,[46] Lemos and colleagues,[47] Slottow and colleagues,[48] and Kornowski and colleagues,[49] and of those that included a composite MACE endpoint (all except Slottow and colleagues), it was found that DES significantly reduced the occurrence of adverse events. As noted by Kupferwasser and associates,[46] the DES group tended to receive more intensive medical therapy, involving a higher rate of bifurcation stenting, greater stent length per occluded vessel, and a higher rate of multivessel PCI. This observation suggests that the benefit of TVR reduction with DES may be even greater than the data appear, because these characteristics have been associated with higher rates of TVR.[50,51] Four out of the 5 trials found a significant reduction in TVR with DES, with the exception of Slottow and coworkers,[48] whose results may have been confounded by differences among treatment groups, as the BMS group had a larger average vessel diameter and shorter stent length, which may place them at a lower risk for stenosis. Kornowski and coworkers[49] observed a significant reduction in the individual safety endpoint of recurrent MI (0% DES vs 6.1% BMS; $P = .02$), and a nonsignificant tendency toward a lower incidence of stent thrombosis in the DES group (0.8% DES vs 3.6% BMS).

Overall, among the registry studies conducted on the use of DES in STEMI, none observed a significant increase in stent thrombosis and most demonstrated a significant reduction in TVR with DES compared with BMS.

Among studies with longer follow-up periods (averaging between 1 and 2 years), there are conflicting results concerning the reduction in TVR and effect on mortality of DES implantation in STEMI patients. The REAL (Registro Regionale AngiopLastiche Emilia-Romagna) registry demonstrated a significant reduction in MACE, death, and repeat revascularization.[52] Through the use of propensity score analysis, this study also confirmed the safety of DES by

Table 5
Main Characteristics of Registry Studies

Study	Stent Type	DES/BMS (N)	Follow-Up (mo)	Antiplatelet Duration, DES (mo)
Bose R et al.[58]	PES	115/18	12-28	6
Bose R et al.[58]	SES	55/18	12-28	3
Cheneau E et al.[45]	SES	103/504	6	1
GRACE[53]	PES and SES	1313/3780	24	< 6
Hannan EL et al.[56]	PES and SES	1154/772	18 (mean)	-
Jensen LO et al.[59]	PES and SES	783/2973	15	12
Kornowski R et al.[49]	PES and SES	122/506	12	12
Kukreja N et al.[65]	PES	1022/531	38 (median)	3
Kukreja N et al.[65]	SES	185/531	38 (median)	3
Kupferwasser LI et al.[46]	PES and SES	131/130	12	3-12
Lemos PA et al.[47]	SES	186/183	10	3
Mauri L et al.[61]	PES and SES	4016/3201	24	Unable to determine
MIDAS[62]	PES and SES	5719/5399	24	-
REAL[52]	SES	205/1412	13 (mean)	3
RESEARCH/T-SEARCH[15]	PES	136/183	36	5.7 (mean)
RESEARCH/T-SEARCH[15]	SES	186/183	36	4.2 (mean)
Romano M et al.[60]	PES and SES	120/250	24 (mean)	6-12
Shishehbor MH et al.[57]	PES and SES	344/355	20 (mean)	-
Slottow TL et al.[48]	PES and SES	122/122	12	12
STENT[63]	PES and SES	1292/548	9	Unable to determine
STENT[63]	PES and SES	663/335	24	Unable to determine
Vlaar PJ et al.[64]	PES and SES	552/577	12	6
Vlaar PJ et al.[64]	PES and SES	552/577	24	6

BMS, bare metal stent; DES, drug-eluting stent; GRACE, Global Registry of Acute Coronary Events; MIDAS, Myocardial Infarction Data Acquisition System; PES, paclitaxel-eluting stent; REAL; Registro Regionale AngiopLastiche Emilia-Romagna; SES, sirolimus-eluting stent; RESEARCH/T-SEARCH, Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital/Taxus-Stent Evaluated at Rotterdam Cardiology Hospital; STENT, Strategic Transcatheter Evaluation of New Therapies.

finding no difference in the rates of stent thrombosis among treatment groups. In contrast, the GRACE (Global Registry of Acute Coronary Events) registry, which did not measure TVR as an endpoint, had complex findings regarding differences in mortality for different time points during follow-up.[53] Though the mortality at 2-year follow-up was significantly lower in the DES group (3.9% vs 5.3% for BMS; $P = .04$), during the period from 6 months to 2 years following PCI, survival became significantly reduced in the DES group compared with the BMS group (6.3% vs 1.6% for BMS; $P < .01$). Because antiplatelet therapy was discontinued at or before 6 months in nearly half of the patients in both treatment groups, it is thought that an increase in stent thrombosis in the DES group may have caused the change in relative survival rates. However, the GRACE registry divided its patients into those receiving all BMS and those receiving at least 1 DES during their single intervention, implying that some patients in the DES group also received BMS during the same procedure. Because of this lack of complete separation between treatment groups, it is impossible to determine whether the difference in results between the 2 groups is entirely due to the difference in stent type. It has been shown that stent thrombosis occurs with BMS as well as DES,[54,55] so no definitive conclusions can be drawn from the increase in mortality documented, as there is overlap in treatment types.

Table 6
Registry Studies Data

	Stent Thrombosis (%)			TVR (%)			Death (%)			Myocardial Infarction (%)			Safety Endpoint (%)		
Study Name	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**	**DES**	**BMS**	***P* Value**
Bose R et al.[58 a]	1[b]	0[b]	NS	7	0	NS	4.3	5.6	NS	0	0	NS	6	5.5	NS
Bose R et al.[58 c]	0[b]	0[b]	NS	7.2	0	NS	1.8	5.6	NS	1.8	0	NS	7	5.5	NS
Cheneau E et al.[45]	0	0	1	1	10.3	.014	7	11	.14	1	2	.7	9	24	< .001
GRACE[53]	-	-	-	-	-	-	3.9	5.3	.04	2.5	2	.26	-	-	-
Hannan EL et al.[56]	-	-	-	-	-	-	5	8.6	.007	-	-	-	-	-	-
Jensen LO et al.[59]	3.6	3.6	.96	7.2[d]	8.7[d]	.09[d]	7.8	11.4	.09	6	4.9	.47	6	4.9	.28
Kornowski R et al.[49]	0.8	3.6	.07	5.7	15.2	.006	3.3	7.1	.1	0	6.1	.02	11.5	21.3	.01
Kukreja N et al.[65 a]	3.4	1.9	NS	6.9	8	NS	12.9	16.4	NS	5.6	5.7	NS	21.5	25	NS
Kukreja N et al.[65 c]	3.2	1.9	NS	7	8	NS	11.4	16.4	NS	3.8	5.7	NS	17.8	25	.04
Kupferwasser LI et al.[46]	0.8	1.6	.56	3.1	14.3	.002	7.8	9.5	.66	1.6	6.3	.051	9.4	23.8	.002
Lemos PA et al.[47]	0	1.6	.1	1.1	8.2	< .01	8.3	8.2	.8	8.8	10.4	.5	9.4	17	.02
Mauri L et al.[61]	-	-	-	10.2	13.9	.003	8.5	11.6	.008	7	8	.34	-	-	-
MIDAS[62]	-	-	-	-	-	-	9.8	14.8	.0001	-	-	-	-	-	-
REAL[52]	1	1.5	.8	2.8	5.4	.01	6.2	12.8	.02	4.8	3.1	.3	14	20.3	.03
RESEARCH/T-SEARCH[15 a]	2.9	1.6	NS	7.7	12	.3	12.4	13.3	.78	4.7	3.5	.62	20.6	25.5	NS
RESEARCH/T-SEARCH[15 c]	2.7	1.6	NS	8	12	.12	11.5	13.3	.63	4	3.5	.99	17.9	25.5	NS
Romano M et al.[60]	2.6[b]	2.8[b]	.6[b]	0.8	9.2	< .001	0.8	1.3	.5	4.3	6.9	.4	0.8	1.3	.5
Shishehbor MH et al.[57]	-	-	-	9[d]	14[d]	.04[d]	9	9	.67	-	-	-	17	22	.05
Slottow TL et al.[48]	0.8	0	NS	8.7	7	.637	9.2	13.3	.307	4.4	5.3	.757	-	-	-
STENT[63 e]	1	2.7	.039	4	7.5	.014	6.3	8.4	.683	1.6	5.5	.453	11.3	17.2	.094
STENT[63 f]	1.8	3.9	.105	8	11.3	.02	8	13.7	.332	5	6.9	.969	17.7	25.7	.065
Vlaar PJ et al.[64 g]	-	-	-	6.2	10.4	.002	3.7	4.2	.93	2.7	4.3	.31	9.1	15.3	.18
Vlaar PJ et al.[64 f]	-	-	-	7.7	11.5	.002	6.4	6.4	.93	7.2	5.6	.31	16.3	18.8	.18

BMS, bare metal stent; DES, drug-eluting stent; GRACE, Global Registry of Acute Coronary Events; MIDAS, Myocardial Infarction Data Acquisition System; NS, not significant; REAL; Registro Regionale AngiopLastiche Emilia-Romagna; RESEARCH/T-SEARCH, Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital/Taxus-Stent Evaluated at Rotterdam Cardiology Hospital; TVR, target vessel revascularization; STENT, Strategic Transcatheter Evaluation of New Therapies.
[a]Results from paclitaxel-eluting stent arm.
[b]The value given is late stent thrombosis only.
[c]Results from sirolimus-eluting stent arm.
[d]The value given is target lesion revascularization, not TVR.
[e]Results from 9-month follow-up.
[f]Results from 24-month follow-up.
[g]Results from 12-month follow-up.

The registry study by Hannan and colleagues,[56] which followed patients for an average of 18 months, also focused on safety and did not include the TVR efficacy endpoint. In their study, which separated patients into those receiving only BMS and those receiving only DES, a decrease in mortality was observed with the use of DES (5% vs 8.6% for BMS; $P = .007$). A small-scale registry study by Shishehbor and associates[57] found significant reductions in TLR and the composite safety endpoint (death and TLR) with DES, though there was no difference in mortality rate between the treatment groups during the period of follow-up, which averaged 20 months. Neither of these studies included stent thrombosis as an endpoint. Though there

appears to be conflicting evidence from these studies regarding the effect of DES on mortality, the studies with complete separations between treatment groups support the safety of DES.

Other studies with 1- to 2-year follow-up periods have been unable to demonstrate significant differences between DES and BMS for any endpoint. A single-center retrospective study by Bose and coauthors[58] observed MACE and stent thrombosis rates that were consistent with those reported in earlier randomized trials, but their study was not sufficiently powered to achieve statistical significance for either endpoint. Patients treated with SES and PES were analyzed separately, but no differences between DES groups could be distinguished. A larger study by Jensen and associates[59] observed that patients treated with DES tended to have lower rates of TLR and death (P = .09 for both). This study also observed no difference between DES and BMS in the rate of stent thrombosis even after 15 months of follow-up.

Among registries that followed patients for 2 years, there is agreement about the benefit of DES in reducing TVR, but different studies had conflicting results regarding the potential safety benefits of DES. These studies, conducted by Romano and colleagues,[60] Mauri and associates,[61] and the MIDAS (Myocardial Infarction Data Acquisition System) study group,[62] also did not find any increased safety risk associated with DES for the endpoints studied. The single-center registry analyzed by Romano and colleagues[60] provided data that demonstrated a significant decrease in TVR with DES compared with BMS without any increased incidence of stent thrombosis, death, or reinfarction. Additionally, patients treated with DES experienced a significantly lower rate of MACE (P = .01), which was thought to be due in part to the lower TVR rate. The propensity-score matching analysis of Massachusetts' mandated PCI database conducted by Mauri and associates[61] reinforced the safety and efficacy benefits associated with DES in a much larger patient population with 2 years of follow-up. In addition to a significant decrease in the need for repeat revascularization in the DES group, patients had a significantly lower mortality rate (8.5% vs 11.6% for BMS; P = .008). This study also analyzed data from patients with non-STEMI, and similarly found that mortality rates were lower in patients treated with DES (12.8% vs 15.6%; P = .04). There was no significant difference in the rate of reinfarction between STEMI patient groups treated with DES and BMS (7.0% vs 8.0% for BMS; P = .34). Although unobserved confounders are an important limitation to registry studies analyzed with propensity-score matching, Mauri and associates[61] included a broader scope of possible confounders. They also performed sensitivity analyses, such as analyzing the outcomes 2 days after PCI, which would be too early for the DES to convey any measurable benefit, to determine whether any residual confounding variables existed. The MIDAS registry focused on the difference in mortality rate between DES and BMS and did not analyze for the efficacy endpoints of revascularization, stent thrombosis, or recurrent MI. In the 1118 patients included in this study, there was a significant reduction in mortality associated with DES at the 2-year follow-up (9.8% vs 14.8% for BMS; P = .0001).

Other registry studies analyzed data at multiple durations of follow-up to compare short- and long-term results, but found few differences in results between different follow-up durations. The STENT (Strategic Transcatheter Evaluation of New Therapies) registry performed propensity score analysis for different populations of patients at 9 and 24 months after PCI, and the results support the safety and efficacy of DES.[63] At both time points, there are significant reductions in the need for revascularization in the DES group without any associated increase in risk of adverse events such as death, MI, or stent thrombosis. An unexpected result was observed for stent thrombosis at the 9-month follow-up, as DES were associated with a significantly lower rate of stent thrombosis (1% vs 2.7% for BMS, P = .039). Between 1 and 2 years after stent implantation, stent thrombosis increased in the DES group to surpass the rate in the BMS group, but not to a significant degree (DES = 1.1%, BMS = 0.3%, P = .28). An analysis of the Mayo Clinic registry followed up with the same group of patients after 1 and 2 years post-PCI.[64] The only significant difference detected between the DES and BMS groups was a marked reduction in TVR for patients treated with DES that remained at 2-year follow-up (P = .002 at both 1- and 2-year follow-up). Rates of death, recurrent MI, and MACE were comparable between groups at both time points, though there was a trend toward fewer MACE in the DES group. The findings from this study supported the conclusion that DES are effective and safe for use in the treatment of STEMI patients, although stent thrombosis was not tested as a safety endpoint.

There are 2 registry studies that followed patients for a duration of 3 years or more, and both separated DES patients into groups treated with either PES or SES. Neither long-term study demonstrated a significant

sustained reduction in TVR with DES compared with BMS, and although one observed a significant reduction in MACE with DES, the other found a trend toward a higher risk of stent thrombosis with DES compared with BMS. The RESEARCH/T-SEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital/ Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registry study analyzed data from 505 patients and did not find a significant difference in TVR between DES and BMS.[15] It appeared that a reduction in TVR with DES, which was significant after 1 year for SES, was lost by the third year of follow-up. The safety endpoints did not differ significantly between treatment groups, but the cumulative rate of stent thrombosis had a tendency to be higher in the SES and PES groups during the 36-month follow-up. However, the patients for whom data were analyzed in this study underwent an average duration of 4 to 6 months of antiplatelet therapy, which is much shorter than the current guideline of 12 months for patients receiving DES. This premature discontinuation of clopidogrel therapy may have contributed to the increase in the rate of stent thrombosis, and may have contributed to the loss of the beneficial reduction in TVR. Because this is a relatively small-scale study, a lack of power may partially explain the findings of nonsignificance for the clinical endpoints, particularly TVR. Another long-term study was conducted by Kukreja and colleagues,[65] which followed patients who underwent primary PCI for STEMI for an average duration of 38 months. They found no significant differences among BMS, SES, and PES groups, except for a decrease in MACE in patients treated with SES. Though there were no significant differences in the rates of early, late, or total stent thromboses, the only patients who experienced very late stent thrombosis were in the DES groups (2.7% of SES and 0.9% in PES, both significant). Kukreja and colleagues[65] hypothesize that part of the lack of beneficial TVR reduction in their DES population may be due to the "real-world" aspect of the study. Most randomized trials, the results of which strongly support the conclusion of reduced revascularization with DES, exclude patients with certain presentations, such as bifurcation lesions, tortuous or calcified vessels, cardiogenic shock, or left main coronary artery disease. As these patients were included in registry studies such as RESEARCH/ T-SEARCH and the analysis conducted by Kukreja and colleagues, their outcomes may have altered the observed benefits and risks associated with DES in comparison with BMS.

There is conflicting evidence emerging from the several registry studies that have been conducted to determine the safety risks and efficacy benefits that may be associated with the use of DES in STEMI patients. However, the majority of findings support the conclusion that DES are safe and effective at treating patients with STEMI. However, more definitive conclusions about the long-term outcomes associated with DES will require large randomized trials with follow-up periods that extend beyond 2 years.

Sirolimus Versus Paclitaxel

SES and PES are the most widely used classes of DES, and were initially proven safe and effective in the SIRIUS (Sirolimus-coated BX VELOCITY Balloon-Expandable Stent in the Treatment of Patients With De Novo Coronary Artery Lesions)[10] and TAXUS-IV (Polymer-Based Paclitaxel-Eluting Stent in Patients With Coronary Artery Disease)[11] trials, respectively. These drugs are known to have very different mechanisms of action in inhibiting inflammation and cell proliferation to reduce restenosis and target vessel revascularization. Sirolimus acts by binding to FK506-binding protein 12 (FKBP12), and this complex binds to and inhibits the mammalian target of rapamycin (mTOR), which arrests the cell cycle in late G_1, halting subsequent smooth muscle growth. This early arrest of the cell cycle allows sirolimus to inhibit many different targets that play a role in restenosis.[66] Paclitaxel affects microtubule polymerization by stabilizing and promoting assembly of microtubules, which reduces the proliferation of vascular tissue, signal transduction, and cell migration.[67] This inhibition of microtubule depolymerization arrests the cell cycle in the G_1/M and G_0/G_1 phases.[68]

A meta-analysis published by Kittleson and coworkers[69] in 2005 found that SES results in a larger reduction in TLR than PES, although a sensitivity analysis of the odds ratios for TLR with SES and PES revealed no significant difference. The trials included in this meta-analysis compared an individual class of DES with BMS, so there were no data available that compared SES to PES directly. Therefore, the difference in the absolute reduction in TLR may have been due in part to the type of BMS used in the trials. Simonton and associates[70] addressed this concern by conducting a study of the STENT registry, analyzing data from 9226 patients treated with PES or SES and minimizing confounding variables with propensity score matching. In this "real-world" population, there was no significant difference between the 2 types of DES in the

incidence of adverse events such as TVR and MACE after 9 months of follow-up. The REWARDS (Registry Experience at the Washington Hospital Center with Drug Eluting Stents) registry found that patients treated with SES had much higher rates of stent thrombosis than PES patients, but there was no difference in the rate of MACE after 1 year of follow-up.[71] One possible explanation for the higher stent thrombosis rate with SES is that guidelines at the time only recommended 3 months of clopidogrel therapy with SES but 6 months with PES, which may have led to an increase in stent thrombosis that was not due to stent choice. The opposite was observed in a meta-analysis of 14 trials that investigated the incidence of late stent thrombosis, which found that late stent thrombosis was more frequent in the PES group than in the SES group, and least frequent in the BMS group.[72] Significant differences in late stent thrombosis occurring more than 6 months after the procedure were present in the comparisons between SES and BMS (0.51% PES vs 0% BMS; $P = .025$) and between the combined DES and BMS (0.44% DES vs 0.06% BMS; $P = .014$), but the difference between SES and BMS was not significant (0.35% SES vs 0.14% BMS; $P = .33$). Among randomized, controlled trials there are conflicting results, as most studies found no meaningful difference in outcomes between SES and PES groups with follow-up periods of up to 3 years,[73-75] but some single-center trials such as SIRTAX (Sirolimus-eluting Stent Compared With Paclitaxel-eluting Stent for Coronary Revascularization) observed a significant reduction in MACE with SES. After 9 months of follow-up, the SIRTAX trial demonstrated that the PES group had significantly higher rates of MACE than patients treated with SES (10.8% PES vs 6.2% SES; $P = .009$), which was attributed to lower rates of angiographic restenosis (11.7% PES vs 6.6% SES; $P = .02$) and TLR (8.3% PES vs 4.8% SES; $P = .03$).[76] A meta-analysis by Schömig and coworkers[77] observed a reduction in reintervention rate and stent thrombosis with SES compared with PES, and PES patients had a slightly higher risk of recurrent MI. However, individual patient data were not available for all 16 trials that were analyzed. Definitive conclusions regarding which type of DES is safer or more effective than the other will require large randomized, controlled trials with long follow-up periods.

Studies comparing PES to SES specifically in patients with STEMI have also been conducted. Park and colleagues[78] examined clinical outcomes after 1 year and angiographic results after 6 months in Korean patients treated with SES and PES, and found that SES patients had lower late lumen loss after 6 months, but no clinical difference was observed at 1 year. Juwana and associates[79] observed the same trends in their trial with follow-up to 1 year in which all patients received clopidogrel for at least 6 months, as there was no significant difference between SES and PES for any clinical endpoint, but restenosis and in-stent late loss were significantly lower in the SES group. The multicenter PROSIT (Prospective Randomized Comparison of Sirolimus- Versus Paclitaxel-Eluting Stents for the Treatment of Acute STEMI) study[80] observed a similar reduction in in-segment late loss with SES compared with PES, as well as decreased in-segment restenosis. They noted that SES tended to have a lower incidence of MACE than PES patients after 1 year ($P = .07$). Some of the trials and studies discussed earlier analyzed patients treated with SES or PES as separate patient groups. The PASEO trial[37] divided DES patients based on whether they were to receive SES or PES, but only analyzed the data comparing each DES to BMS, and did not draw any conclusions from comparing SES to PES directly. However, in examining the data, it appears that SES were associated with slightly lower rates of stent thrombosis and TLR, although these differences do not appear to be significant (stent thrombosis rates of 5.6% for PES vs 3.3% for SES at 2-year follow-up). Neither the registry study by Bose and coauthors[58] nor the RESEARCH/T-SEARCH study[15] observed significant differences in outcomes such as stent thrombosis, TVR, and MACE between SES and PES. The registry study by Kukreja and colleagues[65] found an advantage with SES for the MACE endpoint, as SES were observed to significantly reduce MACE compared with BMS, but PES did not. However, the reduction of MACE with SES compared with PES directly was not statistically significant ($P = .09$). From these results, it appears that implantation of one type of DES confers no advantage in terms of clinical outcomes over the use of the other.

Alternative Drug-Eluting Stents

The ENDEAVOR II (Randomized Comparison of the Endeavor Abt-578 Drug Eluting Stent With a Bare Metal Stent for Coronary Revascularization) trial demonstrated a reduction in clinical and angiographic restenosis with zotarolimus-eluting stents (ZES) compared with BMS during 24 months of follow-up.[81] The ENDEAVOR III (Randomized Comparison of Zotarolimus-Eluting and Sirolimus-Eluting Stents in Patients

With Coronary Artery Disease-3) trial reported that ZES resulted in significantly higher in-segment late loss and restenosis than SES after 8 months of follow-up, but was not sufficiently powered to evaluate clinical endpoints.[82] Both trials excluded patients experiencing a recent (within 72 hours) MI, so giving ZES to STEMI patients would be considered an off-label use. Jain and associates[83] completed a study of the E-Five (E-Five: To Evaluate the 'Real World' Clinical Performance of the Medtronic Endeavor ABT-578 Eluting Coronary Stent System; A Prospective, Multicenter Registry), a global multicenter registry that included data from patients who have received ZES, and did not exclude patients with STEMI. Data were analyzed for the 30-day follow-up, and the MACE rates were similar to those observed in the ENDEAVOR trials and low enough to suggest that ZES may be safe for STEMI patients, but stronger conclusions may be drawn after the 12 months of follow-up are completed.

Biolimus is also a sirolimus analog, and was compared with SES in the LEADERS (Limus Eluted From a Durable Versus Erodable Stent Coating) noninferiority trial.[84] This study included patients experiencing acute coronary syndromes such as non-STEMI and STEMI, and found that after 9 months of follow-up, biodegradable polymer biolimus-eluting stents were noninferior to durable polymer SES for the combined MACE endpoint.

The immunosuppressant tacrolimus has also been formulated as a non-polymer coated DES, and has been tested for efficacy at reducing restenosis.[85] Because the polymer coating used to deliver paclitaxel and sirolimus from conventional DES has been thought to contribute to late stent thrombosis, a DES that does not require the polymer coating, like tacrolimus, might offer an improvement in the safety of DES, especially in patients with acute coronary syndrome. The TEST (Tacrolimus-Eluting Stent) registry[86] reported a high rate of binary restenosis (39.4%) with tacrolimus-eluting stents after angiographic follow-up at 8 months post-PCI. After 22 months of clinical follow-up, there were high rates of MACE (40.9%), target lesion revascularization (31.5%), MI (11%), and death (5.5%), which indicated poor long-term outcomes with tacrolimus-eluting stents. Rinker and coworkers[87] tested the safety and efficacy of tacrolimus-eluting stents in patients with acute coronary syndromes with an angiographic follow-up 6 months after implantation, and the results similarly showed a high rate of restenosis and late lumen loss.

Main Points

- Stent placement in patients with ST-elevation myocardial infarction (STEMI) improves outcomes more favorably than balloon angioplasty alone by decreasing the rates of restenosis and target vessel revascularization (TVR). Drug-eluting stents (DES) further decrease the incidence of restenosis and have been found to be safe for most presenting situations, as they do not significantly increase the risk of stent thrombosis, death, or recurrent myocardial infarction (MI) when compared with bare metal stents (BMS). Sirolimus- (SES) and paclitaxel-eluting stents (PES) are the most widely used classes of DES.
- One long-term observational study suggested that the use of DES may increase the incidence of stent thrombosis after 3 years of follow-up, at which point the beneficial reduction of TVR is lost due to the additional procedures required to treat the stent thromboses.
- The incidence of stent thrombosis in STEMI patients treated with DES has been shown to increase with premature discontinuation of dual antiplatelet therapy. Guidelines released by the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions recommend that dual antiplatelet therapy be continued for at least 12 months after DES implantation to reduce the risk of stent thrombosis.
- Results from many small- to moderate-scale randomized trials support the assertion that DES reduces rates of TVR and binary restenosis without significantly impacting safety endpoints such as recurrent MI and death. Some results even suggest that DES improves safety by reducing the rate of major adverse cardiac events (MACE).
- Studies comparing PES to SES specifically in patients with STEMI have been conducted; no significant difference between SES and PES for any clinical endpoint was found, but restenosis and in-stent late loss were significantly lower in the SES-treated group. SES were associated with slightly lower rates of stent thrombosis and MACE.
- Reaching a conclusion about the safety and efficacy of DES in the treatment of STEMI requires long-term follow-up and large patient cohorts that have sufficient power to delineate statistically significant differences in safety endpoints.

Everolimus, a sirolimus derivative that is formulated with a new polymer, is thought to cause less inflammation compared with other drugs used for DES. Everolimus-eluting stents (EES) were analyzed in an unselected population in the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) registry (including patients with acute coronary syndromes) and their safety and efficacy were compared with that of BMS, PES, and SES.[88] The results at the 6-month follow-up suggested that EES were as safe and effective as BMS, PES, and SES, and may even be more effective than BMS and PES. The SPIRIT III (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de novo Native Coronary Artery Lesions) trial randomized patients to receive either PES or EES.[89] Their results showed that EES patients required fewer revascularization procedures, experienced less late lumen loss, and had lower MACE rates than PES patients. Between 1 and 2 years of follow-up, stent thrombosis occurred less frequently in the EES group, and after the 2 years of follow-up, there was a 45% reduction in MACE and 32% reduction in target vessel failure in patients treated with EES. This DES appears very promising at reducing adverse events after PCI, but patients with acute coronary syndromes were excluded from the SPIRIT III trial. Further trials will be necessary to determine if the safety and efficacy extend to this patient population, who would benefit greatly from a reduction in stent thrombosis rates.

Conclusions

Stent choice for patients with acute MI has been intensely debated since DES became widely used for both approved and off-label uses. Though the literature contains evidence that cautions against the use of DES in MI patients for reasons such as an elevated rate of stent thrombosis, especially late stent thrombosis, a review of the trials, meta-analyses, and registry data supports the safety of DES. Overall, the data suggest that DES appear to be safe in MI as there is no consistent indication that DES are associated with a higher risk of stent thrombosis compared with BMS. In terms of efficacy, the vast majority of data support the conclusion that DES reduce the rate of TVR but do not increase the rate of death and MI in patients with MI. Ultimately, large randomized clinical trials with long-term follow-up are required to assess the true safety and efficacy of DES in patients with MI. ■

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References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. 2003;361:13-20.
2. Zhu MM, Feit A, Chadow H, et al. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials. *Am J Cardiol*. 2001;88:297-301.
3. De Luca G, Suryapranata H, Stone GW, et al. Coronary stenting versus balloon angioplasty for acute myocardial infarction: a meta-regression analysis of randomized trials. *Int J Cardiol*. 2008;126:37-44.
4. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol*. 2007;50:463-470.
5. Moreno R, Fernández C, Hernández R, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol*. 2005;45:954-959.
6. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356:1030-1039.
7. Spaulding C, Daemen J, Boersma E, et al. A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356:989-997.
8. Mauri L, Silbaugh TS, Wolf RE, et al. Long-term clinical outcomes after drug-eluting and bare-metal stenting in Massachusetts. *Circulation*. 2008;118:1817-1827.
9. Roukoz H, Bavry AA, Sarkees ML, et al. Comprehensive meta-analysis on drug-eluting stents versus bare-metal stents during extended follow-up. *Am J Med*. 2009;122:581.e1-e10.
10. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315-1323.
11. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation*. 2004;109:1942-1947.
12. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA*. 2007;297:2001-2009.
13. Lüscher TF, Steffel J, Eberli FR, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. *Circulation*. 2007;115:1051-1058.
14. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation*. 2008;118:1138-1145.
15. Daemen J, Tanimoto S, García-García HM, et al. Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction (from the RESEARCH and T-SEARCH Registries). *Am J Cardiol*. 2007;99:1027-1032.
16. De Luca G, Stone GW, Suryapranata H, et al. Efficacy and safety of drug-eluting stents in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *Int J Cardiol*. 2009;133:213-222.
17. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344-2351.
18. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) phase II trial. *N Engl J Med*. 1989;320:618-627.
19. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126-2130.
20. Park DW, Park SW, Park KH, et al. Frequency of and risk factors for stent thrombosis after drug-eluting stent implantation during long-term follow-up. *Am J Cardiol*. 2006;98:352-356.
21. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation*. 2007;115:2426-2434.

22. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol*. 2008;51:172-209.
23. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al; the BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents. *J Am Coll Cardiol*. 2006;48:2584-2591.
24. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356: 998-1008.
25. Valgimigli M, Percoco G, Malagutti P, et al; the STRATEGY Investigators. Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA*. 2005;293:2109-2117.
26. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N Engl J Med*. 2006;355:1105-1113.
27. Díaz de la Llera LS, Ballesteros S, Nevado J, et al. Sirolimus-eluting stents compared with standard stents in the treatment of patients with primary angioplasty. *Am Heart J*. 2007;154: 164.e1-e6.
28. Tierala I, Syvanne M, Kupari M; for the HAAMU study group. Comparison of paclitaxel-eluting with bare-metal stents in acute myocardial infarction. The HAAMU-STENT-study. TCTMD Web site. http://www.tctmd.com/show.aspx?id-56036. Accessed June 20, 2009.
29. van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. *J Am Coll Cardiol*. 2008;51:618-626.
30. Menichelli M, Parma A, Pucci E, et al. Randomized trial of Sirolimus-Eluting Stent Versus Bare-Metal Stent in Acute Myocardial Infarction (SESAMI). *J Am Coll Cardiol*. 2007;49:1924-1930.
31. Siqueira DA, Abizaid AA, Costa Jde R, et al. Late incomplete apposition after drug-eluting stent implantation: incidence and potential for adverse clinical outcomes. *Eur Heart J*. 2007; 28:1304-1309.
32. Kelbaek H, Thuesen L, Helqvist S, et al. Drug-eluting versus bare metal stents in patients with ST-segment elevation myocardial infarction: eight-month follow-up in the Drug Elution and Distal Protection in Acute Myocardial Infarction (DEDICATION) trial. *Circulation*. 2008; 118:1155-1162.
33. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med*. 2006;355: 1093-1104.
34. Valgimigli M, Campo G, Percoco G, et al. Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA*. 2008;299:1788-1799.
35. Stone GW, Lansky AJ, Pocock SJ, et al. Paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction. *N Engl J Med*. 2009;360:1946-1959.
36. Chechi T, Vittori G, Biondi Zoccai GL, et al. Single-Center Randomized Evaluation of Paclitaxel-Eluting Versus Conventional Stent in Acute Myocardial Infarction (SELECTION). *J Interv Cardiol*. 2007;20:282-291.
37. Di Lorenzo E, De Luca G, Sauro R, et al. The PASEO (PaclitAxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) randomized trial. *JACC Cardiovasc Interv*. 2009;2:515-523.
38. Pittl U, Kaiser C, Brunner-La Rocca HP, et al. Safety and efficacy of drug eluting stents versus bare metal stents in primary angioplasty of patients with acute ST-elevation myocardial infarction—a prospective randomized study [abstract]. *Eur Heart J*. 2006;27:650.
39. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation or thienopyridine therapy after drug-eluting stent placement. *Circulation*. 2006;113:2803-2809.
40. De Luca G, Cassetti E, Marino P. Impact of duration of clopidogrel prescription on outcome of DES as compared to BMS in primary angioplasty: a meta-regression analysis of randomized trials. *J Thromb Thrombolysis*. 2009;27: 365-378.
41. Pasceri V, Patti G, Speciale G, et al. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am Heart J*. 2007;153:749-754.
42. Kastrati A, Dibra A, Spaulding C, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J*. 2007;28:2706-2713.
43. Brar SS, Leon MB, Stone GW, et al. Use of drug-eluting stents in acute myocardial infarction: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2009;53:1677-1689.
44. De Luca G, Valgimigli M, Spaulding C, et al. Short- and long-term benefits of sirolimus-eluting stent in ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *J Thromb Thrombolysis*. 2009;28:200-210.
45. Cheneau E, Rha SW, Kuchulakanti PK, et al. Impact of sirolimus-eluting stents on outcomes of patients treated for acute myocardial infarction by primary angioplasty. *Catheter Cardiovasc Interv*. 2005;65:469-472.
46. Kupferwasser LI, Amorn AM, Kapoor N, et al. Comparison of drug-eluting stents with bare metal stents in unselected patients with acute myocardial infarction. *Catheter Cardiovasc Interv*. 2007;70:1-8.
47. Lemos PA, Saia F, Hofma SH, et al. Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol*. 2004;43:704-708.
48. Slottow TL, Steinberg DH, Roy P, et al. Drug-eluting stents are associated with similar cardiovascular outcomes when compared to bare metal stents in the setting of acute myocardial infarction. *Cardiovasc Revasc Med*. 2008;9:24-28.
49. Kornowski R, Vaknin-Assa H, Lev E, et al. Clinical results of drug eluting stents compared to bare metal stents for patients with ST elevation acute myocardial infarction. *Acute Card Care*. 2008;10:167-172.
50. Zahn R, Hamm CW, Schneider S, et al. Incidence and predictors of target vessel revascularization and clinical event rates of the sirolimus-eluting coronary stent (results from the Prospective Multicenter German Cypher Stent Registry). *Am J Cardiol*. 2005;95:1302-1308.
51. Kastrati A, Schömig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol*. 1997;30:1428-1436.
52. Percoco G, Manari A, Guastaroba P, et al. Safety and long-term efficacy of sirolimus eluting stent in st-elevation acute myocardial infarction: the REAL (Registro Regionale AngiopLastiche Emilia-Romagna) registry. *Cardiovasc Drugs Ther*. 2006;20:63-68.
53. Steg PG, Fox KA, Eagle KA, et al; the Global Registry of Acute Coronary Events (GRACE) Investigators. Mortality following placement of drug-eluting and bare-metal stents for ST-segment elevation acute myocardial infarction in the Global Registry of Acute Coronary Events. *Eur Heart J*. 2009;30:321-329.
54. Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. *Circulation*. 2007; 116:2391-2398.
55. Lemesle G, Pinto Slottow TL, Waksman R. Very late stent thrombosis after bare-metal stent implantation: case reports and review of the literature. *J Invasive Cardiol*. 2009;21:E27-E32.
56. Hannan EL, Racz M, Walford G, et al. Drug-eluting versus bare-metal stents in the treatment of patients with st-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2008;1:129-135.
57. Shishehbor MH, Amini R, Oliveria LP, et al. Comparison of drug-eluting stents versus bare-metal stents for treating ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv*. 2008;1:227-234.
58. Bose R, Gupta G, Grayburn PA, et al. Safety of drug-eluting stents in the coronary artery in ST-elevation myocardial infarction at a single high-volume medical center. *Am J Cardiol*. 2007;100:949-952.
59. Jensen LO, Maeng M, Thayssen P, et al. Clinical outcome after primary percutaneous coronary intervention with drug-eluting and bare metal stents in patients with st-segment elevation myocardial infarction. *Circ Cardiovasc Interv*. 2008;1:176-184.
60. Romano M, Buffoli F, Tomasi L, et al. Safety and effectiveness of drug eluting stent in patients with ST elevation myocardial infarction undergoing primary angioplasty. *Catheter Cardiovasc Interv*. 2008;71:759-763.
61. Mauri L, Silbaugh TS, Garg P, et al. Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med*. 2008;359:1330-1342.
62. Vagaonescu TD, Moreyra AE, Wilson AC, et al. Long-term mortality in ST-T segment and non–ST-T segment myocardial infarction after drug-eluting stents and bare metal stents implantation in New Jersey: the MIDAS Registry. Paper presented at: 19th Annual Symposium of Transcatheter and Cardiovascular Therapeutics; October 20-25, 2007; Washington, DC.
63. Brodie BR, Stuckey T, Downey W, et al. Outcomes with drug-eluting stents versus bare metal stents in acute ST-elevation myocardial infarction: results from the Strategic Transcatheter

Evaluation of New Therapies (STENT) Group. *Catheter Cardiovasc Interv*. 2008;72:893-900.
64. Vlaar PJ, Rihal CS, Singh M, et al. Safety and efficacy of drug-eluting stent for ST-segment elevation myocardial infarction in an unselected consecutive cohort. *Catheter Cardiovasc Interv*. 2008;71:764-769.
65. Kukreja N, Onuma Y, García-García H, et al. Primary percutaneous coronary intervention for acute myocardial infarction: long-term outcome after bare metal and drug-eluting stent implantation. *Circ Cardiovasc Interv*. 2008;1:103-110.
66. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part I. *Circulation*. 2003;107:2274-2279.
67. Sollott SJ, Cheng L, Pauly RR, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest*. 1995;95:1869-1876.
68. Sousa JE, Serruys PW, Costa MA. New frontiers in cardiology: drug-eluting stents: Part II. *Circulation*. 2003;107:2383-2389.
69. Kittleson MM, Needham DM, Kim SJ, et al. The efficacy of sirolimus- and paclitaxel-eluting stents: a meta-analysis of randomized controlled trials. *Can J Cardiol*. 2005;21:581-587.
70. Simonton CA, Brodie B, Cheek B, et al. Comparative clinical outcomes of paclitaxel- and sirolimus-eluting stents: results from a large prospective multicenter registry—STENT Group. *J Am Coll Cardiol*. 2007;50:1214-1222.
71. Waksman R, Buch AN, Torguson R, et al. Long-term clinical outcomes and thrombosis rates of sirolimus-eluting versus paclitaxel-eluting stents in an unselected population with coronary artery disease (REWARDS Registry). *Am J Cardiol*. 2007;100:45-51.
72. Bavry AA, Kumbhani DJ, Helton TJ, et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med*. 2006;119:1056-1061.
73. Morice MC, Colombo A, Meier B, et al. Sirolimus- vs paclitaxel-eluting stents in de novo coronary artery lesions: the REALITY trial: a randomized controlled trial. *JAMA*. 2006;295: 895-904.
74. Galløe AM, Thuesen L, Kelbaek H, et al; SORT OUT II Investigators. Comparison of paclitaxel- and sirolimus-eluting stents in everyday clinical practice: the SORT OUT II randomized trial. *JAMA*. 2008;299:409-416.
75. Berger A, Stauffer JC, Seydoux C, et al. Three-year follow-up of the first prospective randomized comparison between paclitaxel and sirolimus stents: the TAXi-LATE trial. *Catheter Cardiovasc Interv*. 2007;70:163-166.
76. Windecker S, Remondino A, Eberli FR, et al. Sirolimus-eluting and paclitaxel-eluting stents for coronary revascularization. *N Engl J Med*. 2005;353:653-662.
77. Schömig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J Am Coll Cardiol*. 2007;50:1373-1380.
78. Park KW, Cho YS, Chung JW, et al. One year clinical and six month angiographic results of drug eluting stents for ST elevation acute myocardial infarction: 'real world' comparison between sirolimus- and paclitaxel-eluting stents. *Int J Cardiol*. 2009;131:350-355.
79. Juwana YB, Suryapranata H, Ottervanger JP, et al. Comparison of rapamycin- and paclitaxel-eluting stents in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Am J Cardiol*. 2009;104:205-209.
80. Lee JH, Kim HS, Lee SW, et al. Prospective randomized comparison of sirolimus- versus paclitaxel-eluting stents for the treatment of acute ST-elevation myocardial infarction: pROSIT trial. *Catheter Cardiovasc Interv*. 2008; 72:25-32.
81. Fajadet J, Wijns W, Laarman GJ, et al. Randomized, double-blind, multicenter study of the Endeavor zotarolimus-eluting phosphorylcholine-encapsulated stent for treatment of native coronary artery lesions: clinical and angiographic results of the ENDEAVOR II trial. *Circulation*. 2006;114:798-806.
82. Kandzari DE, Leon MB, Popma JJ, et al. Comparison of zotarolimus-eluting and sirolimus-eluting stents in patients with native coronary artery disease: a randomized controlled trial. *J Am Coll Cardiol*. 2006;48:2440-2447.
83. Jain AK, Meredith IT, Lotan C, et al. Real-world safety and efficacy of the endeavor zotarolimus-eluting stent: early data from the E-Five Registry. *Am J Cardiol*. 2007;100(suppl):77M-83M.
84. Windecker S, Serruys PW, Wandel S, et al. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomized non-inferiority trial. *Lancet*. 2008;372:1163-1173.
85. Daemen J, Serruys PW. Drug-eluting stent update 2007: part II: unsettled issues. *Circulation*. 2007;116:961-968.
86. Tamburino C, Di Salvo ME, Capodanno D, et al. Real world safety and efficacy of the Janus tacrolimus-eluting stent: long-term clinical outcome and angiographic findings from the Tacrolimus-Eluting STent (TEST) registry. *Catheter Cardiovasc Interv*. 2009;73:243-248.
87. Rinker A, Nusser T, Grossman G, et al. Angiographic results of a tacrolimus-eluting stent in acute coronary syndrome lesions. *Clin Res Cardiol*. 2009;98:89-93.
88. Onuma Y, Kukreja N, Piazza N, et al. The everolimus-eluting stent in real-world patients: 6-month follow-up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) Registry. *J Am Coll Cardiol*. 2009;54:269-275.
89. Stone GW, Midei M, Newman W, et al. Randomized comparison of everolimus-eluting and paclitaxel-eluting stents: two-year clinical follow-up from the Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions (SPIRIT) III trial. *Circulation*. 2009;119:680-686.