

# Drug-eluting stents: a comprehensive appraisal

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Cardiovascular medicine has evolved over the last few decades, with the advent of percutaneous interventional treatments. In particular, balloon angioplasty and, subsequently, coronary stenting has revolutionized our current perspective of stable and unstable coronary artery disease management. However, the long-term results of stent usage have been blighted by the dual problems of in-stent restenosis and stent thrombosis. Whilst stent thrombosis became much less frequent with the introduction of dual-antiplatelet therapy, restenosis remained a significant problem. Intense work on stent development has successfully led to the introduction of drug-eluting stents (DES) in an effort to address this problem. Randomized trials have consistently proven the superior efficacy of DES over bare metal stents, in elective patients, acute coronary syndromes and patients with diabetes mellitus. Nevertheless, the routine use of DES in by-pass venous graft disease remains debatable. The initial DES used sirolimus and paclitaxel are now being joined by newer stents releasing drugs, such as everolimus, zotarolimus and tacrolimus. Ongoing developments with the stent platform and the polymer coating are also gradually improving the performance of these stents in clinical practice. More recently, the idea of antibody-coated stents that would encourage epithelialization of stent struts by endothelial progenitor cells recruitment has gained attraction among interventionists, with a possible beneficial impact on reducing the incidence of restenosis.

The treatment of coronary artery disease (CAD) has evolved over the last few decades, especially with the advent of percutaneous coronary intervention. Balloon angioplasty and, subsequently, coronary stenting has revolutionized our current perspective of stable and unstable CAD management [1,2].

Initial results with percutaneous balloon angioplasty only (POBA/PTCA) were encouraging in limited population groups, but periprocedural complications such as plaque rupture and myocardial infarction (MI) concerned interventionists. Moreover, prognostic benefits were also limited by very high rates of restenosis (up to 40%, in some series) [3]. Since restenosis was a major issue for coronary interventions, various supplementary techniques, such as use of laser or rotational atherectomy, were devised to reduce the restenosis incidence. Failure of significant improvement with such devices [4,5] led researchers to focus on the development of scaffolding metal structures called 'stents'.

In this article, we will critically appraise available data on stents, in particular drug-eluting stents (DES) in relation to various circumstances including CAD, patients with diabetes mellitus (DM) and saphenous vein grafts (SVGs). Since in-stent restenosis (ISR) was the main incentive for the development of DES, we shall also

briefly discuss the pathophysiology of ISR, the limitations of currently available DES with the latest evidence and newly emerging devices on the horizon.

## Search strategy

We searched using electronic databases (MEDLINE, EMBASE and DARE) for the words 'drug-eluting stent', 'bare metal stent' (BMS), 'coronary angioplasty' and 'drug-eluting versus BMS'. In addition, abstracts from national and international cardiovascular meetings were studied to identify unpublished studies. Animal studies were not considered.

## Brief historical perspective of stenting

In 1994, two large trials comparing initial metal stents with POBA reported encouraging clinical and angiographic results in favor of stents. In a study of 410 patients, postprocedural incidence of restenosis (31.6 vs 42.1%;  $p = 0.046$ ) and target-vessel revascularization (TVR; 10.2 vs 15.4%;  $p = 0.06$ ) was considerably lower in the stent group compared with those with percutaneous transluminal coronary angioplasty (PTCA) [6]. One European study also favored the stent group as even more impressive results were reported in reduction of restenosis (22 vs 32%;  $p = 0.02$ ) and TVR rates (13.1 vs 22.9%;

## Keywords

- coronary artery disease
- paclitaxel-eluting stent
- randomized, controlled trials
- sirolimus-eluting stent

$p = 0.005$ ) compared with PTCA [7]. Supported by the results from these early moderate-sized studies, the US FDA approved these stents as the first BMS to be used in obstructive coronary disease. Expansion of BMS use in bigger, and wider patient groups allowed audits demonstrating that there were two notable complications of BMS; ISR and stent thrombosis (ST). Although ST incidence reduced with use of dual-antiplatelet therapy, ISR still remains a challenge [8]. Data suggest exceedingly high restenosis (50–60%) and revascularization (30–50%) rates with the use of BMS in high-risk groups, such as those with DM and/or 'high-risk' lesions (e.g., long, narrow and bifurcations) [9].

In the late 1990s, extensive research was carried out to find possible solutions to ISR. Initially, intracoronary radiotherapy or brachytherapy was thought to be a useful way of treating restenosed arteries, but studies suggested restenosis was simply delayed until later and brachytherapy is now seldom used [10]. However, the development of DES during this period was a major breakthrough in interventional cardiology. These stents were based on the concept of local drug release at the site of tissue injury to resist smooth muscle proliferation. Advances in the development of antiproliferative agents and improved stent design to facilitate smooth agent release have caused a dramatic reduction in restenosis and revascularization rates and, therefore, in selected or susceptible cases, DES has become the stent of choice.

#### Instant restenosis & drug-eluting stents

In essence, the pathophysiology of ISR mimics the wound-healing process. Stent deployment causes local vascular injury inducing inflammatory response and smooth muscle cell migration from the media of the vessel to the intima, with subsequent proliferation and matrix hyperplasia [11]. The severity of arterial injury during stent deployment correlates with localized inflammatory response and neointimal growth. Biological data demonstrate vascular recoil, negative tissue remodeling and smooth muscle hyperplasia as three distinct processes in the pathogenesis of ISR [11]. Although tissue recoil and abnormal tissue remodeling (occurring weeks or months after coronary ballooning) were addressed by the development of BMSs [12], smooth muscle proliferation through the stent struts causing ISR remained a major factor in the development of restenosis [13]. These pathological findings provide useful targets for therapies aimed at reducing the incidence of ISR.

The logical approach led to the concept of a device with delivery of inhibitory substances locally to halt smooth muscle cell migration, replication and, ultimately, the reduction of ISR. This concept demanded a stent design, which besides providing metallic support to vascular wall, also provided a drug-delivery medium along with a chemical or substance to inhibit muscular hyperplasia. These components were crucial in the success of DES as it has been demonstrated that stent metallic configuration is directly related to effective delivery of the drug [14,15]. Similarly, several stents designs with different types of drug coating have been experimented for DES. Some drugs, such as paclitaxel, can be coated directly on a metal stent, but the majority of the agents must be attached to a polymer, which acts as a drug reservoir [16].

Many drugs have been tested in both animals and humans and most have reduced the incidence of ISR. However, the mechanism(s) of action are different and more than one mechanism may be present. For example, tacrolimus, sirolimus and everolimus are some of the antiproliferative agents used, and all inhibit DNA synthesis. Others, such as batimastat and halofuginone, predominantly target smooth muscle migration [17]; whilst others, such as CD34 antibody-coated stents cells, attract endothelial progenitor cells to enhance postdeployment endothelialization [17,18]. The Cypher® (Cordis Corporation, USA; sirolimus-eluting [SES]) stent, and Taxus® (Boston Scientific Corporation, USA; paclitaxel-eluting [PES]) stent, were the first two approved stents and have been extensively used in randomized trials, which all demonstrate significant reductions in ISR rates (TABLES 1 & 2).

#### Sirolimus-eluting stent versus bare metal stent in native coronary artery disease

The SES (Cypher) was the first approved DES by the FDA in April 2003. This is a stent that is based on a BMS and is coated with a layer of polymer incorporating sirolimus and releasing it by diffusion. The safety and efficacy of SES has been studied in several trials against BMS or PES in different clinical circumstances (e.g., acute coronary syndrome, SVG and DM). Some randomized, controlled trials (RCTs) suggest that the SES may be superior to PES. Nonetheless, the evidence of the risk of restenosis with SES use in single CAD is more extensive compared with scarce data on SES use in complex coronary lesion. The landmark RCTs comparing SES with BMS are summarized in TABLE 1.

Table 1. Sirolimus-eluting stent versus bare metal stent.

Author	n	DM (%)	Study design	Primary outcome	Findings	Comments	Ref.
Morice <i>et al.</i> (2002)	238	19	Single lesions in native coronary arteries, diameter: 2.5–3.5 mm and length: ≤18 mm	In-stent LLL	Lower in-stent LLL (p < 0.001) in SES	Double-blind study and no ST event in either arm	[19]
Moses <i>et al.</i> (2003)	1058	26	Native coronary artery lesion, diameter: 2.5–3.5 mm and length: 15–30 mm	TVR, combination of cardiac death and AMI	TVR in BMS and SES was 16.6 and 4.1%, respectively (p < 0.001).	Multicenter, double-blind study and high frequency of diabetics	[20]
Schofer <i>et al.</i> (2003)	352	23	Single native coronary artery disease, diameter: 2.5–3.0 mm and length: 15–32 mm	MLD	MLD was significantly higher in SES (2.22 vs 1.33; p ≤ 0.0001)	Multicenter, double-blind, targeted small caliber and long lesions.	[21]
Schampaert <i>et al.</i> (2004)	100	24	Long (15–32 mm) and small (2.5–3.0 mm) <i>de novo</i> coronary artery lesions	MLD	TVR (p < 0.05) and MLD was 65% higher in SES than BMS (p < 0.001)	Double-blind, multicenter study, demonstrated efficacy of SES in small arteries	[22]
Ardissino <i>et al.</i> (2004)	257	25	Native coronary disease, diameter: <2.75 mm and length: <33 mm	Binary in-segment restenosis	Restenosis rate in BMS and SES was 53.1 and 8.9%, respectively (p < .001)	Stable and ACS patients, single-blinded and multicenter study	[23]
Pache <i>et al.</i> (2005)	500	31	Native coronary disease of all sizes	≥50% stenosis	SES had lower stenosis rate (8.3 vs 25.5%) and TVR (7.2 vs 18.8%)	BMS with thin struts were used	[24]
Ortolani <i>et al.</i> (2007)	104	16	Critical <i>de novo</i> coronary artery stenosis, lesion length: ≤28 mm, but all diameters	In-stent LLL	In-stent LLL was significantly lower in SES group (0.18 ± 0.40 mm vs 0.58 ± 0.51 mm; p < 0.001)	No clinical difference between the two groups at 12 months	[25]
Kelbaek <i>et al.</i> (2006)	322	18	Complex coronary disease (or bifurcation, ostial location or angulation), lesion diameter: 2.25–24.50 mm and length: ≥15 mm	MLD	Stenosis in SES vs BMS was 19.3 vs 43.8%, respectively (p < 0.001)	MACE in SES versus BMS was 4.3 vs 29.3%, respectively. ST in SES vs BMS was 0.6 vs 3.1%, respectively	[26]
Suttorp <i>et al.</i> (2006)	200	13	CTO and all lesion sizes	Binary in-segment restenosis	Restenosis rate in SES vs BMS was 7 vs 36%, respectively (p < 0.001)	Significantly lower rates of TVR, TVF and MACEs	[27]

ACS: Acute coronary syndrome; BMS: Bare metal stent; CTO: Chronic total occlusion; DES: Drug-eluting stent; DM: Diabetes mellitus; LLL: Late lumen loss; MACE: Major cardiac adverse events; MI: Myocardial infarction; MLD: Minimum luminal diameter; SES: Sirolimus-eluting stent; ST: Stent thrombosis; TVF: Target-vessel failure; TVR: Target-vessel revascularization.

Table 2. Paclitaxel-eluting stent versus bare metal stent.

Author	n	DM (%)	Study design	Primary outcome	Findings	Comments	Ref.
Grube <i>et al.</i> (2003)	61	18	De novo or restenotic lesions, diameter: 3–3.5 mm and length: ≤12 mm	Combination of death, acute MI, TVR and ST	MACE in PES and BMS was 3 and 10%, respectively	Multicenter, double-blind study	[29]
Colombo <i>et al.</i> (2003)	536	15	Native single coronary lesion, diameter: 3–3.5 mm and length: ≤12 mm	6 month ISR measured by IVUS	ISR was lower in SR (7.9%), MR (7.8%) compared with BMS (23%)	Multicenter study and lower incidence of cardiovascular events in DES group	[30]
Stone <i>et al.</i> (2004)	1314	32	Native coronary lesion, diameter: 2.5–3.75 mm and length: 10–28 mm	TVR and MACE	73% relative reduction in TVR rate in DES group	Multicenter study, no difference in ST in both groups and insignificant reduction in 12-month risk of MI and cardiac death	[31]
Stone <i>et al.</i> (2005)	1156	32	Native coronary lesion, diameter: 2.25–4 mm and length: 10–46 mm	TVR and MACE	Significant TVR reduction of 8.6% in PES compared with 17.7% in BMS	Large, double-blind study but noncomplex CAD and slow release PES use	[32]
Dawkins <i>et al.</i> (2005)	444	20	Native coronary disease, diameter: 2.5–3.75 mm and length: 10–46 mm	TVR and MACE	TVR is significantly lower in PES (18.9 vs 6.8% in BMS and PES, respectively)	Double-blind study	[33]
Erglis <i>et al.</i> (2007)	103	12	Left main stem disease, diameter: 3.74–73.82 mm and length: 8–28 mm	TVR and MACE	MACE in BMS and PES was 70% and 87%, respectively, at 6 months follow-up (insignificant)	Pretreatment with cutting balloon owing to unprotected LMS	[34]

BMS: Bare metal stent; DES: Drug-eluting stent; DM: Diabetes mellitus; IVUS: Intravascular ultrasound; LMS: Left main stem; MACE: Major cardiac adverse events; MI: Myocardial infarction; MR: Moderate release; PES: Paclitaxel-eluting stent; SR: Slow release; ST: Stent thrombosis; TVF: Target-vessel failure; TVR: Target-vessel revascularization.

The Randomized Study with the Sirolimus-Eluting Velocity Balloon-Expandable Stent (RAVEL) was the first Cypher study where the efficacy of SES was investigated by demonstrating lower in-stent late lumen loss (LLL) compared with BMS [19]. In this moderate-sized cohort of 238 patients where diabetics (19%) and females (37%) were under-represented, the use of the SES led to better angiographic outcomes, although clinical outcomes were not measured as primary outcomes.

To address this issue, a much larger trial, the Sirolimus-Eluting Stent in *De Novo* Native Coronary Lesions (SIRIUS) was launched [20]. In this double-blind study of 1058 patients, where clinical outcomes were investigated as primary end points but a greater proportion of diabetics were also included. This study recruited many complex CADs as 23% of all treated lesions were type C lesions (by American Heart Association/American College of Cardiology [ACC/AHA] guidelines) and 42% had multi-vessel coronary disease. Although recruitment from 53 centers would have some individual variations, the overall results were strongly in favor of Cypher. Target-vessel failure (TVF; 8.6 vs 21%) and TVR (4.1 vs 16.6%) rates were much lower compared with BMS (all  $p < 0.001$ ).

Furthermore, results from the European SIRUS [21], Canadian SIRUS [22] and Sirolimus-Eluting and an Uncoated Stent in the Prevention of Restenosis in Small Coronary Arteries (SES-SMART) studies [23] also demonstrate favorable results with the use of SES. Since the risk of restenosis is more pronounced in smaller vessels, all three studies recruited patients with lesions between 2.5 and 3.0 mm.

With the ongoing development in DES, concurrently extensive work was also carried out to improve the efficacy of BMSs. In a trial by Pache *et al.*, the SES was randomized against BMS with thinner struts hypothesizing that BMS with thinner struts could be equally useful compared with SES [24]. Binary restenosis was investigated as primary outcome in this cohort of 500 patients at the end of 6 months postdeployment. The restenosis rate was 25.5% in BMS compared with 8.3% in SES. Similarly, TVR was also significantly lower in DES group ( $p < 0.001$ ). Nevertheless, this remains debatable as, more recently, Ortolani *et al.* also studied a similar but smaller cohort and found no significant difference was demonstrated between the two groups, thus, “it remains to be seen whether the angiographic superiority of SES can translate into clinical superiority” [25].

Whereas cumulative evidence suggests Cypher (SES) is a safer and more efficacious option, data on its use in complex CAD are more limited. In the Stenting Coronary Arteries in Non-stress/Benestent Disease (SCANDSTENT) trial, Kelbaek *et al.* recruited 322 patients with complex CAD (36% chronic total occlusions [CTOs], 34% bifurcations and 22% ostial lesions), and 6-month luminal loss and major adverse cardiac events (MACEs) were found to be significantly lower in the DES group ( $p < 0.001$ ). Moreover, no difference was observed in incidence of ST in both groups [26]. Furthermore, the Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II) study randomized SES or BMS in 200 patients with CTO [27]. Like SCANDSTENT, there were fewer diabetics (13%) in this trial, but an equal percentage of CTOs of all coronary arteries was represented in this study. Furthermore, when compared with the BMS, lower rates of TVR and MACE (composite cardiovascular mortality, MI, heart failure, TVR and target lesion revascularization) were demonstrated with reduction in the incidence of binary stenosis (7 vs 36%;  $p < 0.001$ ). Indeed, this study favored the use of SES, whereas other DES stents have not been randomized in a CTO cohort.

#### **Paclitaxel-eluting stent versus bare metal stent in native coronary artery disease**

The PES (TAXUS) is based on a BMS and is coated with a reservoir polymer-delivering paclitaxel. Based upon the drug release, slow-, moderate- and fast-release formulations were launched but only the first two have been used in clinical trials [28]. A number of RCTs have compared PES in native CAD with BMS and other formulations of DES, such as SES (TABLE 2).

TAXUS 1 was a feasibility study comparing PES and BMS in 61 patients with single native CAD lesion [29]. Promising results regarding its safety and tolerability have led to a larger study of 561 patients [30]. In this double-blinded trial, patients were randomized to moderate- or slow-release PES or BMS. The aim was also to compare the efficacy between the two PES formulations, although fast-release stents were not randomized. Intravascular ultrasound (IVUS)-based assessment of in-stent volume loss, angiographic restenosis and MACE (composite cardiovascular mortality, MI, heart failure, TVR and target lesion revascularization) were significantly lower in PES groups compared with BMS group (all  $p < 0.0001$ ). Moreover, no difference was noted between each PES formulation. In addition, this study was more focused on primary lesions

in native coronary arteries, excluding complex lesions. Both the aforementioned studies were of moderate size and the prevalence of diabetics was only 15–18%.

Later in the TAXUS IV trial, a much larger cohort ( $n=1314$ ) was recruited with higher percentage of diabetics (32%) [31]. In this trial, moderate-sized native coronary *de novo* lesions were stented either with BMS or PES in matched groups. After a follow-up period of 12 months, PES use was associated with a relative reduction in TVR (62%), TVF (53%) and MACE (49%), better figures than in the BMS arm. Another similar study of 1156 patients who were blindly randomized to slow-release PES or BMS stent [32] found angiographic restenosis was significantly lower in the PES group (33.9–18.9%), and TVR reduction was less pronounced compared with previous studies (17.3–12.1%;  $p = 0.02$ ).

Safety data for complex lesions with PES use led to the double-blind, multicenter TAXUS VI study [33]. This study included 444 patients with long and complex coronary lesions (55.6% were classified as type C of the AHA/ACC) and randomized to moderate-release Taxus or BMS. A relative risk reduction of 53% in TVR in the PES group compared with BMS was noted ( $p = 0.0027$ ), but there were no significant differences between the incidence of MACE between two groups. This study further encouraged the trialists for more widespread use of TAXUS in complex lesions.

In 2007, in a study of 103 patients with unprotected left main-stem lesions were randomized to either PES or BMS under IVUS guidance [34]. Follow-up analysis demonstrated binary restenosis in 22% of BMS and 6% of PES patients ( $p = 0.021$ ). By IVUS at 6 months, the percentage of neointimal volume obstruction was reduced with PES ( $p = 0.02$ ). Furthermore, the MACE-free survival rate was 70% in BMS and 87% in PES patients ( $p = 0.036$ ).

#### **Paclitaxel-eluting stents versus sirolimus-eluting stents in native coronary artery disease**

Data from studies comparing SES or PES against BMS demonstrated remarkable reductions in restenosis rates as well as incidence of TVR and reinfarction. Although event rates dropped markedly, different DES types might still differ in clinical event rates. Thus, further randomized comparisons between different formulations of DES to detect any beneficial effects confined to any type. TABLE 3 summarizes some of the prominent trials.

Table 3. Paclitaxel-eluting stent versus sirolimus-eluting stent.

Author	n	DM (%)	Study design		Primary outcome	Findings	Comments	Ref.
			Disease type	Lesion length (mm)				
Kastrati <i>et al.</i> (2005)	200	29	Stable CAD	No restriction	Binary restenosis	Significantly lower risk of TVR in SES group	Acute MI not included in study	[35]
Goy <i>et al.</i> (2005)	202	34	ACS	No restriction	MACE	No difference was found in either group	Lower rate of TVR in both groups	[36]
Windecker <i>et al.</i> (2005)	1012	20	Stable CAD and ACS	No restriction	Composite of MACE (death, MI and TVR)	Rate of MACE in SES and PES was 6.2 and 10.8%, respectively (p = 0.009)	Insignificantly higher rate of death in PES group	[37]
Galløe <i>et al.</i> (2008)	2098	16	STEMI, NSTEMI and USA	No restriction	MACE, TVR and composite of cardiac deaths	No significant difference in PES and SES in primary and secondary end points	Large, blinded study and real-world cases selection	[38]
Morice <i>et al.</i> (2006)	1386	28	SA or USA but no MI	>15	Binary restenosis	Binary stenosis was in 9.6% of patients with SES vs 11.2% in PES (p = 0.31)	Exclusion of acute MI	[39]
Petronio <i>et al.</i> (2008)	100	25	Stable CAD	≥16	Neointimal hyperplasia	Lower neointimal hyperplasia in SES vs PES (p < 0.001)	Acute MI not included in study	[101]

ACS: Acute coronary syndrome; BMS: Bare metal stent; CAD: Coronary artery disease; MACE: Major cardiac adverse events; MI: Myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; PES: Paclitaxel-eluting stent; SA: Stable angina; SES: Sirolimus-eluting stent; ST: Stent thrombosis; STEMI: ST-elevation myocardial infarction; TVR: Target-vessel revascularization; USA: Unstable angina.

Initial small studies, such as the Intracoronary Stenting or Angioplasty for Restenosis Reduction – Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE), randomized 200 patients to PES, SES and POBA [35] and, overall, demonstrated a much lower rate of restenosis in stent group when compared with POBA. However, an analysis between the PES and SES groups did not demonstrate any significant difference between either group in causing angiographically detectable restenosis (p = 0.19). In the TAXi trial, a higher percentage of diabetics was included (34%) to investigate MACE, but no significant difference was found [36].

The Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) study, which was a much larger study of 1012 patients, clearly demonstrated favorable results with the use of SES [37]. A lower MACE (6.2 vs 10.8%; p = 0.0009), lower mortality and TVR rates was noted with SES compared with PES, respectively. More recently, the large Danish Organization on Randomized Trials with Clinical Outcome (SORT OUT II) reported no differences with use of SES or PES in unstable CAD patients. At 9-month follow-up, MACE rates were similar in both the Cypher and Taxus groups (7.8 vs 8.6%, respectively; p = nonsignificant) [38]. Similar results in stable CAD patients were found in the REALITY trial of 1386 patients [39]. In both of these trials, patients with DM were a minority, being 15 and 28%, respectively.

Owing to a broad variability among different studies, the choice between SES or PES remains generally undecided; the current guidance is to use DES where BMS is not indicated, such as in patients with DM with a high risk of restenosis [201].

### Drug-eluting stents in special circumstances

#### ST-elevation myocardial infarction

In the primary percutaneous coronary angioplasty (PCI) setting, the incidence of ISR has been reported in up to 27% of patients [40]. A number of RCTs have demonstrated clinical effectiveness, tolerability and restenosis risk reduction with DES compared with BMS in stable CAD. Data on the use of DES in ST-elevation myocardial infarction (STEMI) were relatively limited until recently, and some of the more recent large trials are given in TABLE 4.

In a study investigating 712 patients with STEMI undergoing primary PCI, Spaulding *et al.* randomized study population to SES or

Table 4. Drug-eluting stents in ST-elevation myocardial infarction.

Author	n	DM (%)	Design	Lesion length (mm)	Lesion diameter (mm)	Primary outcome	Findings	Comments	Ref.
Spaulding <i>et al.</i> (2007)	712	16	SES vs BMS	≤30	2.25–23.50	Combination of vessel-related death, AMI and TVR	Primary end points lower in SES group (7.3 vs 14.3%; p = 0.004)	Single-blinded, 48 centers and 1-year follow-up	[41]
Menichelli <i>et al.</i> (2008)	320	21	SES vs BMS	No restriction	No restriction	Binary stenosis	Stenosis was lower in SES (9.3 vs 21.3%; p = 0.032)	Significant reduction of TVR and MACE	[42]
van der Hoeven <i>et al.</i> (2006)	310	9.7	SES vs BMS	No restriction	No restriction	In-segment LLL	In-segment LLL was 0.68 ± 0.57 in BMS group and 0.12 ± 0.43 in SES group	Rates of death, MI and ST were not different and high rate of late stent malpositioning	[43]
Laarman <i>et al.</i> (2005)	619	11	PES vs BMS	No restriction	>2.5	Composite of death of cardiac cause (recurrent MI or TVR)	Statistically insignificant change in primary outcomes	1% annual incidence of ST in each group	[44]
Hofma <i>et al.</i> (2005)	322	11	SES vs PES	No restriction	No restriction	MACE	Similar all-cause mortality in both groups, better TVR in favor of SES in 30 days and no difference at 1 year	Similar 1-year survival rates	[45]
Lee <i>et al.</i> (2008)	308	26	SES vs PES	No restriction	No restriction	MACE and TVR	Both primary end points were lower in SES but did not reach significance	Only two cases of ST in the PES group and significantly lower in-stent LLL in SES	[46]

AMI: acute myocardial infarction; BMS: bare metal stent; DM: diabetes mellitus; LLL: late lumen loss; MACE: major cardiac adverse events; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; ST: stent thrombosis; TVR: target-vessel revascularization.

Table 5. Drug-eluting stent in diabetes mellitus.

Author	n	Design	Lesion length (mm)	Lesion diameter (mm)	Primary outcome	Findings	Comments	Ref.
Sabate <i>et al.</i> (2007)	160	SES vs BMS	No restriction	<4.0	In-segment LLL	Significant reduction in primary outcome ( $p < 0.001$ )	TVR and MACE also reduced in SES (31.3 vs 7.3% and 36.3 vs 11.3%, respectively; both $p < 0.001$ )	[55]
Baumgart <i>et al.</i> (2008)	200	SES vs BMS	$\leq 42$	2.5–3.5	In-segment LLL	LLL in 8.8% of SES and in 42.1% in BMS ( $p < 0.0001$ ).	No ST at 1 year, equal efficacy in all types of diabetes	[56]
Ortolani <i>et al.</i> (2005)	1648	DES vs BMS	>9mm	No restriction	MACE	Lower MACE with DES vs BMS (22.5 vs 28.1%, respectively; $p = 0.01$ )	Benefits limited to noninsulin-dependent patients	[57]
Dibra <i>et al.</i> (2008)	250	PES vs SES	No restriction	No restriction	In-segment LLL	Greater in-stent LLL in PES vs SES ( $p = 0.002$ )	Higher TVR rates in PES, but did not reach significance	[58]
Lee <i>et al.</i> (2005)	400	PES vs SES	>2.4	>12	ISR	ISR (3.4 vs 18.2%; $p < 0.001$ ) and TVR (2.0 vs 7.5%; $p = 0.017$ ) was significantly lower in SES	SES is better than PES in 1-year follow-up in diabetics	[59]

BMS: Bare metal stent; DES: Drug-eluting stent; ISR: In-stent restenosis; LLL: Late luminal loss; MACE: Major cardiac adverse events; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; ST: Stent thrombosis; TVR: Target-vessel revascularization.

BMS [41] and found that the overall primary end point was significantly better with DES than with BMS (7.3 vs 14.3%). No significant difference in mortality, reinfarction and ST was found between two groups. The presence of DM was reported as a major determinant of restenosis, but yet again only 16% of the study population was diabetic. A similarly designed trial, the Sirolimus Stent Versus Bare Stent in Acute MI (SESAMI) study also randomized 320 patients with acute STEMI to SES or BMS in order to investigate the 1 year risk of stenosis [42]. Contrary to the study by Spaulding *et al.*, the study population had a much wider lesion inclusion criteria, and relative reductions of 56, 61 and 62% were noted in binary stenosis, TVR and MACE, respectively. Recently published results from the MISSION! trial, which randomized SES against BMS in 310 STEMI patients, demonstrated a significant reduction in in-stent LLL ( $p < 0.001$ ); however no difference was observed in the risk of MI, mortality and ST [43]. Data are still lacking on long-term follow-up, as all the aforementioned trials were usually confined to a 1-year follow-up period.

Studies investigating PES individually against BMS are relatively less common in STEMI settings. For example, Laarman *et al.* investigated 619 patients with STEMI between PES or BMS [44], but the difference between the stent arms did not reach statistical significance.

Although data from trials of SES against PES in stable CAD suggest the superiority of SES, no major clinical trial, thus far, has clearly concluded the superiority of SES or PES in ACS. In 2005, Hofma *et al.* investigated 136 patients with STEMI who were randomized to SES or PES [45]; although 30-day mortality was similar in both the groups, there was significantly reduced TVR in favor of SES, but no difference was demonstrable at 1 year. In a larger study of 308 patients, no significant difference between SES or PES was observed [46].

So the question is, given the current evidence, which is the right stent that should be used in STEMI? Should we use a DES or BMS, and if a DES is used, which formulation is best? These questions may have been answered by a meta-analysis of eight large RCTs comparing DES with BMS in STEMI [47], which concluded that DES was better in STEMI than BMS as there were significantly fewer numbers of reinterventions in the DES group during follow-up. However, there was no significant difference in ST, MI

or death between the two groups. Owing to the very nature of eluting agents, the vascular healing response may be delayed. Autopsy data from CVPath registry have demonstrated that DES implantation was substantially linked to delayed endothelialization [48]. Moreover, the Global Registry of ACE (GRACE) registry did not report significant difference at 6- and 12-month follow-up, but there was a worse prognosis compared with BMS after 1 year [49]. Hence, the choice of stent in STEMI remains quite dependent on clinical circumstances (e.g., DM) and lesion characteristics.

### Diabetes mellitus

Patients with DM carry a higher risk of ISR postcoronary stent deployment compared with nondiabetics [50]. Endothelial dysfunction, platelet dysfunction and abnormal arterial remodeling could be few of the many contributors in the development of ISR [51]. Similarly, diabetics are more likely to have ST, reinfarction and death [52,53].

Since the use of DES, the risk of ISR has considerably reduced in this population (TABLE 5). However, pooled data comparing SES and BMS have been published, raising questions with regard to greater long-term mortality with SES use [54].

More recently, several RCTs in pure diabetic populations have investigated any impact on cardiac events and/or ISR. More studies used SES as the DES for comparisons with BMS and few have randomized PES against BMS.

Sabate *et al.* first randomized SES against BMS in 106 diabetic patients and found a large reduction in in-segment LLL in the SES group ( $0.47 \pm 0.5$  mm vs  $0.06 \pm 0.4$  mm in BMS vs SES, respectively;  $p < 0.001$ ) [55]. Similar results were also reported by Baumgart *et al.* in a study investigating 200 patients [56]. Recently, Ortolani *et al.* reported that although the incidence of MACE was much lower in the DES group compared with the BMS group (22.5 vs 28.5%, respectively;  $p = 0.01$ ), the main benefits were only confined to the noninsulin-dependent diabetic subpopulation [57].

Different types of DES have been compared in the diabetic population. In a study investigating 250 diabetic patients where SES was randomized against PES [58], in-segment LLL was much lower in SES groups, but TVR difference was insignificant. Another similar but larger study of 400 patients also compared DES types [59], which demonstrated a lower incidence of in-segment LLL and ISR rate with

SES, but no difference was found in overall death and reinfarction rate between the two stent groups.

The ultimate revascularization strategy for diabetic patients remains a controversial debate. Whilst some suggest that with DES, the role of coronary artery bypass surgery would be greatly reduced, others argue that there are not enough data from RCTs to support any definite clinical practice guidance for the coronary interventionists [51]. Ongoing clinical trials, such as the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) and Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) would provide much needed answers.

### Vein grafts

Saphenous vein grafts are the most common type of the grafts used in coronary by-pass surgery [60]. Usually 10 years postoperatively atherosclerotic changes start to appear in SVGs, which clinically manifests as the recurrence of angina [61]. In addition to a higher risk of morbidity and mortality, a second operation is technically more difficult, making PCI a more favored method [62].

Although BMS is generally considered the stent of choice, restenosis rates are even higher in SVGs compared with native vessels [63]. The introduction of DES significantly reduced the risk of restenosis compared with BMS in trials of native CAD, however, in most of these trials, SVG lesions have generally been excluded. Therefore, the data are limited and controversial on DES in SVG disease.

Some small studies have randomized SES and PES against BMS in SVG disease (TABLE 6). For example, studies by Agostoni *et al.* [64] and Vermeersch *et al.* [65] investigated neointimal proliferation and in-stent LLL, respectively, in a comparison of SES with BMS; both studies reported SES as a better stent compared with BMS, although subsidiary analysis did not demonstrate any reduction in death or reinfarction [65]. Data comparing PES and BMS in SVG are less clear. Whilst there is a reduction in restenosis and in-stent LLL with SES [66], a similar study found no difference in PES and BMS in reducing MACE [67]. One large study concluded that DES had some marginal benefits over BMS in reducing overall death and TVR after 1 year [68]. However, it also reports that this beneficial impact is less impressive 2 years post-deployment. Another recent study investigating

Table 6. Drug-eluting versus bare metal stent in venous graft disease.

Name	n	DM (%)	Design	Lesion length (mm)	Lesion diameter (mm)	Primary outcome	Findings	Comments	Ref.
Agostoni <i>et al.</i> (2006)	75	13	SES vs BMS	No restriction	2.5–4.0	Neointimal hyperplasia	SES is more effective in inhibiting neointimal hyperplasia	IVUS follow-up	[64]
Vermeersch <i>et al.</i> (2007)	75	15	SES vs BMS	≤66	2.5–4.0	In-stent LLL	In-stent LLL was significantly reduced in SES (0.38 ± 0.51 mm vs 0.79 ± 0.66 mm in BMS; p = 0.001)	TVR reduced, however, death or MI rate unchanged	[65]
Hoffmann <i>et al.</i> (2008)	60	NA	PES vs BMS	<20	2.75–73.5	In-stent LLL, MACE and binary restenosis	Binary restenosis (12 vs 33% in PES and BMS, respectively) and lower MACE rate in PES	Small study, mean venous graft age of 11 years	[66]
Chu <i>et al.</i> (2008)	89	NA	PES vs SES	No restriction	No restriction	MACE	No difference in acute events and death in both groups	Use of distal protection device in all patients	[67]
Gioia <i>et al.</i> (2008)	250	36	DES vs BMS	>14	>2.75	MACE	Lower MACE rate at 1 year but no difference after 2 years	SES, PES and TES were used and high frequency of DM	[68]

BMS: Bare metal stent; DES: Drug-eluting stent; DM: Diabetes mellitus; IVUS: Intravascular ultrasound; LLL: Late luminal loss; MACE: Major cardiac adverse events; MI: Myocardial infarction; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; TES: Tacrolimus-eluting stent; TVR: Target-vessel revascularization.

482 patients found no such beneficial effects within 1 year [69]. Hence, the stent of choice in SVG disease is still uncertain.

### Stent thrombosis & dual-antiplatelet therapy

Stent thrombosis can be a catastrophic phenomenon and, therefore, an apparent increase in the incidence of ST has become a matter of concern for interventionalists. ST has been defined as per protocols and as by the Academic Research Consortium (ARC) depending upon its probability and the time from stent deployment [54]. Contrary to popular belief, ST is not solely linked with DES use. In a large analysis of 20,000 patients, an incidence of 1.2% was reported at 1-month follow-up following BMS [70]. Indeed, the concept behind the development of DES is to suppress intimal growth in order to reduce the risk of stenosis. Whilst DES suppresses neointimal formation, it also impairs the vessel healing process, leading to impaired endothelialization and enhanced blood thrombogenicity due to the prothrombotic effects of eluting substances that contribute to late-DES thrombosis. Data from histological studies suggest that endothelialization is a powerful predictor of ST [71]. Animal models comparing a variety of DES, suggest that new generation of DES especially with thinner struts, may endothelialize rapidly and, thus, may potentially have a much better safety profile [72,73].

From the perspective of interventional cardiology, perhaps the two most important questions are as follows:

- Is ST solely limited to DES group?
- How can this be prevented?

Over time, RCTs comparing DES and BMS have not demonstrated any significant differences in the incidence of ST. Meta-analyses investigating the risk of ST in different types of stents have been summarized in TABLE 7. In a large pooled analysis of 16 randomized trials, DES usage does not have a significantly higher risk of ST, although a reduction in the incidence of MACE and TVR is clearly seen [74]. Several other meta-analyses have also reported indifference between DES and BMS in the causation of ST (TABLE 7).

Furthermore, DM is an independent risk factor for ST [75]; however, no difference has been found in ST between either stent groups [76]. In another meta-analysis, no difference was found in the incidence of acute, late, very late, probable

Table 7. Risk of stent thrombosis in drug-eluting and bare metal stent trials.

Author	Trials	n	Design	ST risk	Comments	Ref.
Spaulding <i>et al.</i> (2005)	4	1748	SES vs BMS	No difference in ST (mortality and MI) incidence rate between two groups	Improved survival in DM patients were noted in subsidiary analysis, although the study was not powered for this	[54]
Kumbhani <i>et al.</i> (2008)	16	2951	DES vs BMS	No significant difference in either group	100% diabetics, less TVR and MACE in DES group ( $p < 0.0001$ )	[74]
Yan <i>et al.</i> (2008)	1 registry	2919	DES vs BMS	No evidence for DES to increase ST risk than BMS	30-day and 1-year ST incidence was noted only and DM and ACS as independent predictors	[75]
Kirtane <i>et al.</i> (2007)	5	3513	PES vs BMS	No difference between BMS (1.2%) or PES (1.4%) and no difference in mortality at 4 years	100% diabetic and PES demonstrated reduction in TVR in a 4-year follow-up (12.4 vs 24.7%; $p < 0.0001$ )	[76]
Stone <i>et al.</i> (2005)	4	3445	PES vs BMS	No difference in the incidence of ST in either group	1% risk of ST across both stent groups	[77]
Pascari <i>et al.</i> (2008)	7	2357	DES vs BMS	ST occurred more frequently in BMS, however it did not reach statistical significance	Only patients with acute MI were included, 12-month follow-up and reduced mortality and TVR in DES group	[80]
Wenaweser <i>et al.</i> (2008)	2	8146	PES vs SES	PES has significantly higher ST risk than SES	4-year follow-up, DM and young age were predictors of ST and concurrent dual antiplatelets for 6–12 months	[81]
Schömig <i>et al.</i> (2006)	16	8695	SES vs PES	Reduced risk in SES without any significant improvement in mortality incidence ( $p = 0.02$ )	Large cohort and mean follow-up 9–37 months	[83]
Mahmud <i>et al.</i> (2007)	13 RCTs plus 16 registries	11000	SES vs PES	Annual risk of ST was 0.55% for SES and 1.48% for PES	100% diabetic patients, revascularization and MACE estimates are similar with both PES and SES	[102]
Mauri <i>et al.</i> (2006)	4	4545	DES vs BMS	No significant difference between two groups	Study was not adequately powered	[103]
Schampaert <i>et al.</i> (2005)	3	1510	DES vs BMS	No evidence for DES to increase ST risk than BMS	Data from SIRIUS, E-SIRIUS and C-SIRIUS, use of SES as DES and improvement in TVR and MACE	[104]
Bavry <i>et al.</i> (2005)	8	3817	DES vs BMS	No evidence for DES to increase ST risk than BMS	Study was limited to 1-year follow-up	[105]

BMS: Bare metal stent; C-SIRIUS: Canadian Sirolimus-Eluting Stent in De Novo Native Coronary Lesions; DES: Drug-eluting stent; DM: Diabetes mellitus; E-SIRIUS: European Sirolimus-Eluting Stent in De Novo Native Coronary Lesions; MACE: Major cardiac adverse events; MI: Myocardial infarction; PES: Paclitaxel-eluting stent; RCT: Randomized, controlled trial; SES: Sirolimus-eluting stent; SIRIUS: Sirolimus-Eluting Stent in De Novo Native Coronary Lesions; ST: Stent thrombosis; TVR: Target-vessel revascularization.

Table 8. New drug-eluting stents on the horizon.

Author	n	DM (%)	Design	Lesion length (mm)	Lesion diameter (mm)	Primary outcome	Findings	Comments	Ref.
Fajadet <i>et al.</i> (2006)	1197	20.1	ZES vs BMS	>9	>2.3	TVF	Significant reduction in TVF (7.9 vs 15.1%) and MACE (7.3 vs 14.4%) in ZES group	Large study, first to demonstrate clinical benefits with ZES vs BMS	[94]
Kandzari <i>et al.</i> (2004)	436	29	ZES vs SES	>14 and ≤27	2.5–3.5	In-stent LLL	ZES had higher in-segment LLL (p < 0.0001) and TVR (p = 0.04) compared with SES	Large, multicenter study demonstrating better results with SES	[95]
Grube <i>et al.</i> (2008)	42	10	EES vs BMS	>6	>2.5	MACE	No difference in MACE in either group	Lower in-segment restenosis in EES group (p < 0.001)	[96]
Stone <i>et al.</i> (2007)	1002	29	EES vs PES	<28	2.5–3.75	In-stent LLL	EES better than PES (p ≤ 0.004)	Significant reduction in MACE in EES group	[97]
Han <i>et al.</i> (2006)	200	22	TES vs BMS in ACS	>16	>2.75	MACE	Lower MACE in TES group (p = 0.038)	Clopidogrel for 4 months postdeployment but no ST, acute MI included	[98]
Co <i>et al.</i> (2007)	120	30	Observation study on genous stent in STEMI patients	>10	>3.0	MACE	MACE was 4.2% at 30 days and 5.8% at 6 months	Use of concomitant thrombus suction devices and GpIIb/IIIa inhibitor	[100]

EES: Everolimus-eluting stent; BMS: Bare metal stent; LLL: Late luminal loss; MACE: Major cardiac adverse events; MI: Myocardial infarction; ST: Stent thrombosis; STEMI: ST-elevation myocardial infarction; TES: Tacrolimus-eluting stent; TVF: Target-vessel failure; TVR: Target-vessel revascularization; ZES: Zotarolimus-eluting stent.

and definite ST in DES and BMS groups after a follow-up of 4 years. However, DES was predictive of subacute ST, based on the ARC classification [54]. Similarly, Stone *et al.* reported a higher incidence of ST in the DES group after 1 year, compared with BMS [77].

Endothelial dysfunction secondary to the eluting agents may be a contributor in the development of stent-related complications. Nevertheless, this concept has been supported by small, nonblinded studies and needs further exploration [78,79]. The procoagulant state in acute MI was also attributed to be another cause of acute ST, and in one comparative analysis of DES and BMS use in STEMI, the BMS carried a nonsignificant trend towards a higher risk of ST [80]. In another large meta-analysis of more than 8000 patients, PES had a significantly higher risk of ST compared with SES [81], although PES appeared to have a significantly lower ST incidence than BMS [82]. Similar results were obtained in another large analysis where patients were followed up for up to 37 months [83].

Although it remains controversial, if the risk of ST is supposed to be equivalent in DES and BMS in short- and long-term studies, this urges the alternative explanation for the pathogenesis of ST. Individual reports indicate that the other 'technical' factors, such as stent malpositioning [84,85] and concurrent drug abuse, for example, cocaine [86], could also be contributors to this problem. Since data investigating predicted stent diameter with IVUS demonstrate that DES and BMS do not achieve 100% of their respective predicted minimum stent areas [87], the stent-deployment technique should be given important consideration as a contributory cause for ST.

Dual-antiplatelet therapy (aspirin and clopidogrel) after DES implantation is crucial as premature discontinuation of antiplatelet drugs and ST has been reported in several anecdotal reports [88]. Although most data do not support major benefits of BMS over DES in reducing risk of ST, the current consensus is that patients noncompliant with dual-antiplatelet therapy regimen should preferably be considered for BMS. However, certain situations, such as surgery or acute bleeding, urge intentional interruption in the dual-antiplatelet therapy. In case of forthcoming surgery, close liaison is needed with the surgical team as the current recommendations are to stop clopidogrel at least 5 days presurgery and to restart 2 days postoperatively. Aspirin should be continued in the interim [85].

Current recommendations are to continue the use of dual-antiplatelet therapy for up to 1 year in patients at low risk for bleeding [89]. However, whether the benefits extend beyond the period of 1 year has not been adequately investigated to support its continuation [90]. More recently, the phenomenon of 'clopidogrel resistance' has been described, whereby more than 50% of the platelets are not inhibited by using clopidogrel and hence, patients remain at high risk of ST despite taking dual-antiplatelet therapy. The AHA/ACC has issued guidelines to increase the dose of clopidogrel prescribed to such patients. The additional use of cilostazol besides aspirin and clopidogrel has been reported to reduce the risk of MACE and ST [91]. Similarly, the TRITON-TIMI 38 trial randomized 12,844 patients to aspirin (75 mg/day) plus clopidogrel (300 mg bolus followed by 75 mg daily) versus aspirin (75 mg/day) plus prasugrel (60 mg bolus followed by 10 mg daily). Subsidiary analysis from this investigation suggests that prasugrel in conjunction with aspirin reduced the incidence of ST both in DES (0.84 vs 2.31%;  $p < 0.0001$ ) and BMS stent (1.27 vs 2.41%;  $p = 0.0009$ ) groups [92].

### Conclusion

The coronary stent was a major breakthrough in the management of CAD. Indeed, ISR was a major limiting factor with BMS in the initial few years until DES was introduced. Since then, various RCTs have compared DES and BMS and have shown significantly reduced ISR, TVR and MACE as end points. Moreover, results from large RCTs in high-risk patients, such as those with DM and STEMI, are also encouraging when compared with BMS, although the role of DES in SVG disease remains debatable. Currently, several DES are commercially available but most data are related to the early stents, such as SES and PES. In large studies, DES has proven significantly better efficacy compared with BMS. Indeed, SES compared with PES has consistently been

reported to have better results in reducing risk of ISR, but whether this translates into better clinical outcome is unknown. Whilst newer DES have been in development, safety data are still rather scarce and need further evaluation.

### Future perspective

In last few years, several eluting drugs have been tested in clinical setting, containing drugs such as everolimus, zotarolimus and tacrolimus. Although initial reports are quite promising, randomized trial data are limited. Most of the clinical trials include rather low-risk lesions yet, in real practice, high-risk lesions such as small diameter and long-segment lesion are frequently observed.

Moreover, some of these new DESs fail to prove their superior effectiveness when compared with older DES, such as the SES. Indeed, the safety data are sparse with newer stents. Recent trials comparing new devices to existing stents are given in TABLE 8.

To illustrate the issues, the zotarolimus-eluting stent (ZES; Endeavor<sup>®</sup>, Medtronic, MN, USA) has shown good safety results from initial feasibility studies [93], and in the ENDEAVOR II trial, 1197 patients were randomized to ZES or BMS [94]. This demonstrated that ZES was superior to BMS as it reduced TVF to 7.9% compared with 15.1% in BMS ( $p = 0.0001$ ) as well as MACE ( $p = 0.0001$ ). When compared with SES in the ENDEAVOR III trial, which included higher frequency of diabetics (29%), the ZES demonstrated worse in-stent LLL compared with SES [95]. Moreover, binary restenosis rate was also much higher for ZES (11.7 vs 4.3%).

Similarly, the everolimus-eluting stent (EES; Xience<sup>™</sup>, Abbot, IL, USA) contains an immunosuppressive and antiproliferative agent and, in animal models, a significant reduction in neointimal proliferation was observed. In a small study of 42 patients [96], the EES was randomized against BMS and demonstrated significantly lower risk of neointimal hyperplasia ( $p < 0.001$ ). The subsequent SPIRIT III was a large EES study of more than a 1000 patients and randomized

### Executive summary

- Advent of drug-eluting stents has revolutionized the management of coronary artery disease owing to significant reduction in incidence of in-stent restenosis.
- Whilst sirolimus- and paclitaxel-eluting stents have proven their superior efficacy over bare metal stents, it remains undecided which formulation of drug-eluting stents is more advantageous in native coronary artery disease.
- Controversial evidence suggest positive trend with the use of drug-eluting stents in high-risk patients (such as patients with diabetes, previous by-pass surgery and ST-elevation myocardial infarction patients).
- Stent thrombosis remains a problem in stent era. However stent thrombosis is not solely associated with bare metal stents. Large meta-analyses have produced controversial results, predominantly suggesting a higher risk with bare metal stents.
- Improved stent design and use of new eluting agents in newer stents in recent trials demonstrates a great futuristic promise.

EES against PES. As a primary outcome, in-segment LLL was much less in EES groups (mean: 0.14 mm) compared with PES (mean: 0.28 mm;  $p < 0.004$ ) [97]. Other eluting substances, such as tacrolimus-eluting stents (TES), are still in the experimental phase. In a small study demonstrating 200 patients, TES marginally showed superiority over BMS [98]. However, the much larger JUPITER II trial (TES vs carbon-coated stent) failed to demonstrate any significant clinical benefits with TES [99]. Thus, the long-term efficacy in reducing restenosis and clinical effectiveness with TES use will require further larger randomized studies.

After favorable results from TRIAS pilot study, recently endothelial progenitor cell capture stent (Genous Bio-Engineered Stent) has

been successfully tested in acute STEMI settings [100]. A large TRIAS registry is currently recruiting patients to test this new stent against all available DES. These stents mediate epithelialization of the struts besides acting as DES and, hence, reduce the risk for restenosis and ST.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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