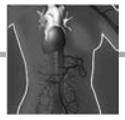
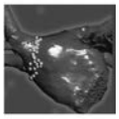
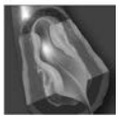

Stent selection in patients with acute coronary syndromes and unstable coronary lesions

Percutaneous coronary intervention (PCI) has been increasingly used over recent years during interventional procedures in patients with acute coronary syndromes including ST-elevation myocardial infarction (STEMI) and non-STEMI. In patients with either STEMI, non-STEMI, high-risk acute coronary syndromes with ECG changes or cardiac enzyme rises, PCI with bare-metal stent (BMS) implantation has been associated with a significant improvement in clinical outcome. Therefore, BMS implantation during primary PCI in STEMI has become a standard of practice. With the introduction of drug-eluting stents (DES) in this decade, the use of these new devices instead of BMS in patients with STEMI has emerged as a rational PCI alternative in this particular subgroup of patients. In spite of the unquestionable benefits of DES in terms of reduction of restenosis and rates of target vessel revascularization, specific concerns have arisen regarding their long-term safety. A high incidence of very late stent thrombosis has been described with these devices and special attention should be paid to patients with unstable coronary lesions, in which plaque composition and remodeling may play a main role in their safety and long-term outcome. Intraluminal thrombus caused by plaque rupture is the most frequent mechanism of STEMI, in which the necrotic core and thin fibrous cap play a major role. In this context, the use of the first DES designs may be futile or even unsafe because delayed healing may further contribute to plaque instability. Adjunctive invasive imaging tools can improve stent deployment and safety outcomes in these lesions with intravascular findings of plaque instability. The introduction of new DES designs with new platforms has minimized many of the safety concerns of the first DES generation, although long-term outcomes with these new DES are pending. Recently, other agents, such as new dedicated anti-thrombotic BMS designs, including self-expanding stents or drug-eluting coated balloons, are exploring their potential indications in patients with acute coronary syndromes and myocardial infarction. Nevertheless, when a patient with an acute myocardial infarction is on the table, our primary aims should be to open the artery safely, preserve muscle, reduce incidence of reinfarction and reocclusion of the infarct-related artery and improve the chances of survival.

KEYWORDS: acute myocardial infarction ■ drug-eluting stents ■ stent thrombosis

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Percutaneous coronary intervention (PCI) has been increasingly used over recent years during interventional procedures in patients with acute coronary syndromes (ACS) including ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) [1–5]. Furthermore, in patients with either STEMI, NSTEMI, high-risk ACS with ECG changes or cardiac enzymes rises, PCI with bare-metal stent (BMS) implantation has been associated with a significant improvement in clinical outcome, including reduction of major adverse cardiac events (MACEs) or recurrent ischemia (Table 1). Importantly, primary PCI during the first hours following the onset of STEMI has been one of the few clinical niches in the field of cardiology, including medical, interventional or surgical approaches, in which an intervention has dramatically reduced the incidence of death and myocardial infarction (MI).

Since the introduction of the first-generation drug-eluting stents (DES) for PCI, sirolimus-eluting stents (SES; CYPHER®, Cordis Corp., NJ, USA) and paclitaxel-eluting stents (TAXUS®, Boston Scientific Corp., MA, USA), the angiographic and clinical parameters of coronary restenosis have decreased noticeably during the first years of follow-up. Several randomized studies comparing BMS with DES in subsets of patients of different complexity have demonstrated a significant reduction in coronary restenosis, which translates into lower rates of target vessel revascularization (TVR) and target lesion revascularization (TLR) [6–11]. However, after several years of systematic use of these devices in a variety of complex subsets of patients in many countries all over the world, angiographic and clinical improvement of the rate of restenosis have not been translated into a reduction of hard cardiac events such as MI

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Table 1. Clinical outcome after angioplasty alone and angioplasty after bare-metal stent implantation in patients with acute myocardial infarction.

	Saito *et al.* [5] n = 136			Rodriguez *et al.* [1] n = 104			Antoniucci *et al.* [2] n = 150			Grines *et al.* [4] n = 900			Suryapranata *et al.* [3] n = 227		
	BMS (%)	*POBA (%)*	*p-value*	*BMS (%)*	*POBA (%)*	*p-value*	*BMS (%)*	*POBA (%)*	*p-value*	*BMS (%)*	*POBA (%)*	*p-value*	*BMS (%)*	*POBA (%)*	*p-value*
	14 days			*30 days*			*30 days*			*6 months*	*30 days*	*6 months*	*6 months*		
Overall death				3.8	7.6	NS	0	4	0.080	3.5	4.2	1.8	2.7	0.15	0.27	2	3	1.00
Cardiac death	3	7	0.261															
Re-ischemia				0	11.5	0.049	2.7	14.7	0.009									
Re-MI	3	4	0.673	0	7.6	NS	1.3	2.7	0.560	0.4	2.4	1.1	2.2	0.29	1.00	1	7	0.036
TVR							1.3	12	0.009	1.3	7.7	3.8	17.0	0.02	<0.001	4	17	0.0016
TLR	6	13	0.161															
Any event	6	19	0.023	3.8	19.2	0.03				4.6	12.6	5.8	20.1	0.46	<0.01	5	20	0.0012

BMS: Bare-metal stent; MI: Myocardial infarction; NS: Not significant; POBA: Plain old balloon angioplasty; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

wand death [12], which raises concerns regarding the true benefits behind the use of DES. Several problems have been associated with the use of DES, including inflammation, delayed endothelial healing, late-acquired stent malapposition (LASMA), collateral circulation damage and endothelial dysfunction [13–20]. Furthermore, the observation that late stent thrombosis is significantly higher after DES implantation [21–25] and that its incremental rate does not decrease over time [26] opens up a question as to its potential role in patients with complex pathological findings, such as those with ACS.

Vulnerable plaque

Most of the ACS, which include unstable angina, two forms of acute MI (AMI) and sudden coronary death, are believed to be the result of luminal thrombosis [27,28]. Plaque rupture is the most frequent cause of luminal thrombosis (60–75% of cases), followed by erosion and calcified nodules [27]. Plaque rupture lesions are characterized by a large necrotic core and an overlying thin disrupted fibrous cap infiltrated with macrophages and T lymphocytes (typically <65 µm) [27,28]. Exposure of the thrombogenic necrotic core to circulating platelets and inflammatory cells results in the formation of a luminal thrombus [27,28]. It is now accepted that the precursor lesion of plaque rupture, which lacks a luminal thrombus, is the vulnerable plaque, also known as thin-cap fibroatheroma (TCFA) [27–29]. The TCFA has a similar, but less pathological, morphology to plaque rupture, with a smaller necrotic core, less calcification and a fibrous cap with fewer macrophages [27].

The complexity of this type of lesion is further underscored by the great degree of heterogeneity in plaque morphology and the composition that one can encounter in a relatively short distance from a given necrotic core, varying from a vulnerable TCFA or a healed rupture to multiple acute ruptures [27]. In this context, the use of DES may be ineffective or even hazardous because delayed healing may further contribute to plaque instability, and systemic pharmacologic treatment may therefore be preferred for the stabilization of vulnerable TCFAs [27]. It has been shown that DES can cause a significant delay in arterial healing characterized by persistent peristrut fibrin deposition, minimal neointimal thickening and incomplete endothelialization compared with BMS [17]. This partial endothelialization and delayed healing may in turn serve as a potent spur of late stent thrombosis associated with DES in AMI

patients [17,20,30]. Culprit lesions in AMI patients treated with DES are associated with a significant delay in healing compared with patients treated with DES for stable angina, suggesting that the underlying plaque morphology plays a major role in the arterial response to DES [20].

Moreover, endothelial dysfunction promotes platelet aggregation, the release of vasoactive mediators and changes in the arterial wall, which have a major role in the progress of coronary artery lesions. The first DES designs have been associated with endothelial dysfunction, in both experimental and clinical studies [14,31–33]; therefore, their use in patients with ACS, in which all of these findings are interrelated, should be indicated with caution.

Several invasive and noninvasive imaging techniques are currently being employed for the early detection and identification of TCFAs before plaque rupture and thrombosis [34,35]. Intravascular ultrasound (IVUS)-based methods such as IVUS-virtual histology, can image the arterial wall, providing real-time information on plaque volume and composition, vessel remodeling, calcification and presence of necrotic core [34–36]. Optical coherence tomography (OCT) is a highly sensitive technique that can produce higher-resolution images than IVUS, from which detailed information about fibrous cap thickness, plaque microarchitecture, macrophage infiltration and thrombus can be extracted [34–36]. More recently, combinations of these tools have been used to enhance the detection of TCFA and lipid-rich plaques. For example, IVUS-virtual histology was combined with OCT for the *in vivo* detection of TCFAs [37,38], which allowed for the first time the identification of the frequency, distribution, morphology and composition of high-risk plaques at bifurcations [38]. Near infrared spectroscopy is now being used as a potential tool for identifying the chemical composition of plaques, with an accurate delineation of their lipid-core content [34,35,39,40]. The use of near infrared spectroscopy can provide additional information for clinical (PCI or coronary bypass graft surgery) and coronary revascularization decisions, such as stent design (DES or BMS) and stent length.

All the aforementioned modalities for the detection of vulnerable lesions are invasive; therefore, only patients with clinical indication for coronary angiography can be treated with these modalities. Conversely, the noninvasive computed tomographic angiography (CTA) technique provides as high a resolution image of the vessel lumen as invasive angiography, but also provides an image of the vessel wall, which grants it with an IVUS-like character that can identify the morphology of unstable plaques [41–43]. The use of CTA for the detection of unstable coronary lesions is exemplified in Figure 1, which shows a large eccentric intermediate mixed lesion with positive remodeling in the right coronary artery (RCA) of a patient detected by CTA but without severe stenosis by conventional angiography. At 2 years, the patient developed a STEMI with a tight lesion (>95%) in the mid-portion of the RCA, corresponding to the previous stenosis detected by CTA. A long BMS was deployed, which involved the proximal and mid portions of the RCA.

Angioplasty with DES implantation in acute coronary syndromes & complex lesions subsets

As previously mentioned, coronary angioplasty with BMS implantation has become the most frequent revascularization strategy in patients with ACS. Moreover, an invasive strategy with PCI has significantly reduced the incidence of MACEs and reinfarction in those patients with ACS having either clinical or ECG markers at high risk (i.e., enzyme or inflammatory marker rise). Randomized clinical trials and registries have not yet established how we can improve these results with the introduction of DES. Despite a significant reduction on TLR, these studies have failed to demonstrate a benefit in the incidence of hard cardiac events associated with DES.

Even though randomized trials advocate the use of DES versus BMS owing to a reduction of instent restenosis [44–50], most of these clinical trials include a well-selected population, use surrogate angiographic end points (e.g., restenosis and instent late luminal diameter loss) and some of them lack long-term outcomes. Moreover, most large randomized studies include TLR rather than TVR in their end points, which favor the results of the DES arm compared with the BMS arm, although the patient's clinical benefit depends on TVR and not on TLR.

Furthermore, results from randomized trials and registries have shown discrepancies, underscoring the selection bias of randomized studies. In fact, many revascularization procedures in those trials have been driven by protocol-mandated coronary angiography. Similarly, in those randomized or observational studies with only clinically driven follow-up angiography, differences in TVR rates were less pronounced, as reported by the Basel Stent Cost–Effectiveness

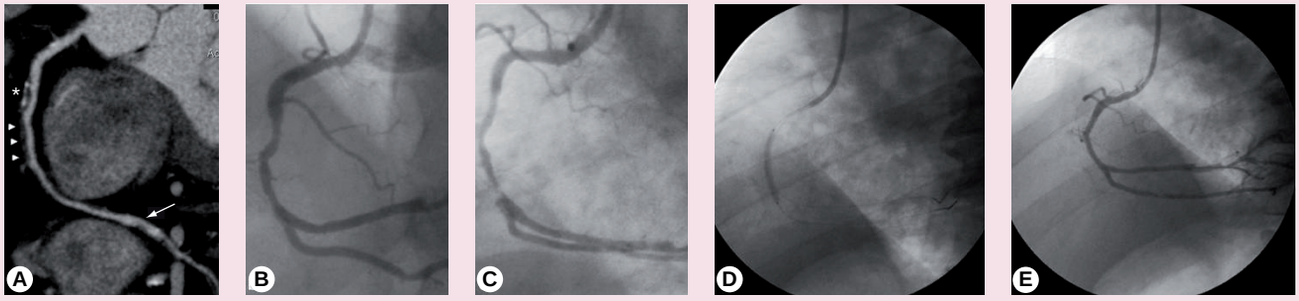

Figure 1. Patient with positive remodeling in the right coronary artery detected by computed tomographic angiography. Patient with positive remodeling in the right coronary artery detected by computed tomographic angiography angiography (asterisk and arrows in **A**), with a nonsevere stenosis in the conventional angiogram **(B)**. A total of 2 years later, an ST-elevation myocardial infarction developed with a tight stenosis in the mid portion of right coronary artery **(C)**, corresponding to the previous stenosis detected in the computed tomographic angiography; a bare-metal stent was succesfully placed **(D & E)**.

Trial – Late Thrombotic Events (BASKET LATE) trial [51] and by two large registries from Sweden [52] and Denmark [53].

We now have new long-term data from randomized trials and registries that raise a question about the real cost–effectiveness of DES in patients with complex lesion subsets [54]. This question regards the case of the diabetic patients included in the Sirolimus-Eluting Stent in *De Novo* Native Coronary Lesions (SIRIUS) trials [55] in which, surprisingly, at 5 years of follow-up, incidence of death and MI were significantly higher in the group treated with SES implantation. In these pooled data, incidence of both death and MI in the diabetic population was significantly higher than in the BMS group after the first year of follow-up. At 4 years of follow-up in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) [52], which included a patient cohort with 80% of either NSTEMI or STEMI, the mortality rate in diabetic patients was found to be significantly higher compared with nondiabetic patients and was independent of the stent design. We do not have a clear explanation for these findings, although diabetic patients have lesions that are more lipid-rich and softer, with more endothelial dysfunction and more prone to rupture than those in nondiabetic populations [56]. All of these pathology findings have also been described as part of the spectrum of ACS. Pathology studies have shown that diabetic plaques are characterized by a larger necrotic core, greater plaque burden and increased macrophage infiltration than those observed in nondiabetic patients, suggesting an increased vulnerability for coronary thrombosis [57,58].

In the Argentine Randomized Study Coronary Angioplasty versus Coronary Bypass Surgery in Multiple Vessel Disease (ERACI) III study [59], which is a nonrandomized comparison from previous BMS and coronary bypass graft surgery randomized data with a prospective registry with DES, a greater incidence of hard cardiac clinical events at 5 years was observed in the DES cohort of patients. Finally, a large registry from Denmark [53], with more than 60% of the patients having ACS, reported a poor 4-year outcome in the DES group, with greater incidence of MI and stent thrombosis, in spite of a reduction in TLR.

These reports also underscore the value of long-term outcomes in patients treated with DES deployment to truly assess the effectiveness of these devices. Notably, some of these studies included a large cohort of patients with ACS, including NSTEMI and STEMI or Braunwald angina class IIIb and IIIc, in which the presence of endothelial dysfunction and plaque rupture plays a major role compared with those with stable clinical conditions. Plaque sealing, less degree of inflammation and complete endothelium stent strut coverage instead of reduction of TVR should be the main goals of stent deployment in patients with unstable coronary lesions with histological characteristics prone to plaque rupture.

Angioplasty with DES implantation in ST-elevation myocardial infarction

Since the introduction of BMS during primary PCI in STEMI [60], which was driven by several randomized studies and registries, BMS implantation has become the standard practice of PCI in patients with STEMI. Both incidence of MACEs and recurrent ischemia have been significantly reduced with the use of BMS in the site of STEMI (Table 1). With the introduction of DES, the use of DES instead of BMS in patients with STEMI has emerged as a rational PCI alternative in this particular subgroup

of patients. Nevertheless, special awareness is needed in this cohort of patients with unstable coronary lesions, in which plaque composition and remodeling can play a main role in their safety long-term outcome.

Several randomized trials have been conducted in recent years exploring the potential advantages of DES in patients with STEMI undergoing PCI [44–50,61–63]. In general, at short- and mid-term follow-up, DES have not been associated with an incremental risk of death and MI, with a sustained benefit in terms of repeated revascularization procedures (Table 2). Nonetheless, special attention to trial design and exclusion criteria should be taken into account before reaching any conclusions [64]. This is testified by the opposing results of two randomized trials regarding whether or not there is an advantage with DES over BMS in TLR or TVR rates, depending on the exclusion criteria [45,61]. Whereas the Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation (PASSION) trial [61], designed with no exclusion criteria, fails to show an advantage in TLR of DES versus BMS at 5 years of follow-up, the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treatment With Balloon Angioplasty (TYPHOON) trial [45], designed with large exclusion criteria, reports an advantage of DES only related to rates of TVR. In addition, 3-year data from the randomized Drug Elution and Distal Protection During Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction (DEDICATION) trial [63] demonstrate that the DES cohort of patients had a greater incidence of all-cause mortality and significantly higher cardiac death compared with those included in the BMS arm.

Late or very late stent thrombosis have been associated with a high incidence of death and MI and may occur especially after discontinuation or reduction of dual antiplatelet therapy (thienopyridines and aspirin) in patients with DES [65–67]. In one registry, after the second year of follow-up, late stent thrombosis was found in 5.3% of STEMI patients treated with DES versus 0.8% in the BMS group [68] and the benefit of DES over BMS in terms of TVR after 3 years was no longer apparent [69]. Late stent thrombosis in patients with STEMI treated with DES seems to be associated with positive arterial remodeling and large thrombus burden [66]; both findings have been linked to the presence of LASMA. Large thrombus burden in patients with STEMI treated with DES has been reported with higher incidence of stent thrombosis (8.2 vs 1.3% with respect to small

Table 2. Clinical outcomes after angioplasty with drug-eluting stent or bare-metal stent implantation in patients with acute myocardial infarction.

Study (duration, patients [n])	Treatment	Overall death	Cardiac death	Re-MI	TVR	TLR	Late ST	Ref.
STRATEGY	DES (%)	8		7	7	6	0	[44]
(8 months, n = 175)	BMS (%)	9		9	20	20	0	
	p-value	0.78		0.60	0.01	0.006	>0.99	
TYPHOON	DES (%)	2.3	2.0	1.1	5.6		0.3	[45]
(1 year, n = 712)	BMS (%)	2.2	1.4	1.4	13.4		0.6	
	p-value	1.00	0.58	1.00	<0.001		1.0	
PASSION	DES (%)	4.6	3.9	1.7		5.3	0.3	[61]
(1 year, n = 619)	BMS (%)	6.5	6.2	2.0		7.8	0	
	p-value	0.30	0.20	0.74		0.23	NS	
MISSION	DES (%)	1.3	1.3	5.7	5.1	3.2	0	[62]
(1 year, n = 310)	BMS (%)	2.6	1.3	9.2	13.2	11.2	0.7	
	p-value	0.44	1.0	0.24	0.01	0.006	0.49	
MULTISTRATEGY	DES (%)	3.0		3.2	3.2			[50]
(8 months, n = 744)	BMS (%)	4.0		4.6	10.2			
	p-value	0.42		0.34	<0.001			
DEDICATION	DES (%)	10.5	6.1	1.9	8.9	6.1		[63]
(3 years, n = 626)	BMS (%)	6.4	1.9	3.2	19.8	16.3		
	p-value	0.084	0.013	0.45	<0.001	<0.001		

BMS: Bare-metal stent; DEDICATION: Drug Elution and Distal Protection During Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction; DES: Drug-eluting stent; MI: Myocardial infarction; MISSION: Prospective Randomized 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-Bolus Dose Tirofiban versus Bare-Metal Stent in Acute Myocardial Infarction; NS: Not significant; PASSION: Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation; ST: Stent thrombosis; STRATEGY: Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent versus Abciximab and Bare-Metal Stent in Myocardial Infarction; TLR: Target lesion revascularization; TVR: Target vessel revascularization; TYPHOON: Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treatment With Balloon Angioplasty.

thrombus burden; p < 0.001) and death and has been independently associated with poor outcome [70].

The Prospective Randomized Trial to Evaluate the Efficacy and Safety of Drug-Eluting Stents versus Bare-Metal Stents for the Treatment of Acute Myocardial Infarction (MISSION! Intervention) trial [62] reports 12.5 versus 37.5% (p < 0.001) of late stent malapposition in STEMI patients with BMS and DES, respectively, with 25% of malappositions in DES patients being acquired during follow-up versus only 5% in BMS patients (p < 0.001). Furthermore, recent OCT studies in DES patients suggest a higher frequency of incompletely apposed and uncovered struts in the STEMI group, and DES implantation was an independent predictor of incomplete stent apposition and the presence of uncovered struts at 6 months of follow-up [71]. Several mechanisms may account for the development of late incomplete stent apposition, including positive remodeling of the vessel wall, decrease in plaque and media owing to resolution of thrombus in patients with STEMI, insufficient stent expansion during implantation and chronic stent recoil [62,66]. However, the first two processes are more likely to be associated with LASMA and appear to be an adverse effect of the drug on the arterial wall in patients treated with DES [62]. The clinical impact of this IVUS observation has been demonstrated by Cook *et al.*, who report a presence of LASMA in 77 versus 12% (p < 0.001) of patients with very late stent thrombosis when compared with the DES control group [66].

The Global Registry of Acute Coronary Events (GRACE) provides insights into mortality outcomes after PCI for STEMI patients receiving BMS only or at least one DES, with up to 2 years of follow-up [65]. This large multinational observational registry in patients with ACS affords very useful information regarding the role of DES in a real-world STEMI population. In spite of hospital mortality being higher for patients receiving BMS than those receiving DES (3.7 vs 2.1%, respectively; p < 0.01), early follow-up mortality (from hospital discharge to 1 year) was the same in both groups and, most importantly, late mortality (from 6 months to 2 years) was significantly higher for patients receiving DES (1.6 vs 6.3%, respectively; p < 0.01). It is worth mentioning that the average GRACE risk score was higher among patients receiving BMS only, indicating that these patients were at a higher risk of death, which may explain the increase in hospital mortality in this group [65]. Overall, this study suggests that there may be an increased risk of late mortality associated with DES in patients with STEMI.

Compliance with long-term dual antiplatelet therapy is also a key issue in patients having PCI during STEMI, because sudden discontinuation of this treatment can have catastrophic effects on poorly healed sites. Despite the apparent awareness of this, the prospective registry of MI patients known as the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) [23] demonstrates that 13.6% of DES patients (~1/7) were not taking this medication 1 month after hospital discharge. Importantly, patients who did not adhere to the medication exhibited an increase in both rate of mortality (7.5 vs 0.7%; p < 0.0001) and frequency of cardiac rehospitalization after 1 year of MI compared with those patients who continued thienopyridine therapy. This raises the possibility of a bias being introduced in controlled clinical trials with selected patients in which prescribed medication and follow-up care is widely available, as opposed to registries representing real world and everyday practice. Moreover, the use of DES is further limited by subgroups of patients that are incompletely responsive, nonresponsive [72] or unsuitable [73] for long-term clopidogrel therapy.

Conclusion

Acute coronary syndromes including unstable angina at rest, NSTEMI and STEMI represent different degrees of a common pathologic finding leading to plaque rupture and thrombosis. PCI clearly plays a major role in the treatment of this cohort of patients. Furthermore, we should proudly recognize that PCI in patients with STEMI is one of the selected clinical circumstances in all of cardiology in which a therapeutic approach has undoubtedly demonstrated a survival advantage.

The role of DES to further improve the results seen with BMS in patients with unstable coronary lesions and STEMI is questionable and currently unknown. Besides the unquestionable advantage in the reduction of coronary restenosis of DES, their safety profile in this cohort of patients is debatable and they could potentially be harmful.

With the introduction of the latest DES designs, new agents have been incorporated into the field, featuring potential solutions for previous adverse effects linked with the first DES generation. Results from these new designs at midterm outcome are promising, although long-term safety outcomes are largely pending.

Vascular healing, less endothelial damage, no endothelium dysfunction, stent struts coverage and so on are the main goals to fulfill when a stent design selection is made for patients with ACS. The introduction of new dedicated BMS with anti-thrombotic layers coating their surface, as well as tailored self-expanding stents, is promising, although these devices still need further exploration. The use of paclitaxel-eluting balloon stents also seems promising, but still requires long-term clinical, angiographic and IVUS data to fully assess its safety profile; in addition, we are also waiting results from randomized studies.

In conclusion, when a patient with an AMI is on the table at the catheterization laboratory, our primary aims should be to open the artery safely, save muscle, preserve ventricular function, reduce incidence of reinfarction and reocclusion of the infarct-related artery and improve survival. All of these primary goals are not linked with restenosis prevention; therefore, these clinical criteria should ultimately drive our stent selection in AMI patients.

Future perspective

The presence of stent thrombosis in patients with ACS and either unstable angina NSTEMI or STEMI is higher compared with stable angina patients, independently of the stent design used [67]. The adverse effects associated with the first DES (late stent thrombosis, delayed healing, inflammation and endothelial dysfunction) and with the old BMS designs (high rate of coronary restenosis and TVR) are currently well known and clearly recognized. Therefore, the question of how we can potentially overcome the negative effects associated with these two stent designs that have large differences in vascular healing profiles remains.

■ New DES designs

During recent years, we have been able to understand the complex process of building the ideal DES design, in which a combination of safety and efficacy should be the main goal. Moreover, we have clearly recognized that minimal luminal diameter loss at follow-up should be reduced to improve late outcome, although the degree of such reduction is contentious [74–76]. Some of the side effects with the first DES designs have been related to the presence of durable polymers [77,78], an essential feature in the first DES generation. The first SES and paclitaxel-eluting stent designs were built using permanent polymers (poly[ethylene-co-vinyl

Table 3. Cardiac major events from trials with new drug-eluting stent designs.

Cardiac event	EUCATAX (n = 422, 1 year) [86]			SPIRIT II (n = 299, 6 months) [81], III (n = 976, 1 year) [82] and IV (n = 3690, 1 year) [83]										LEADERS (n = 1707, 9 months) [84]		
	PES (%)	*BMS* (%)	*p-value*	*TAXUS®* (%)				*XIENCE V®* (%)				*p-value*		*CYPHER®* (%)	*BioMatrix™* (%)	*p-value*
				II	III	IV	II	III	IV	II	III	IV				
Overall death	2.4	3.3	0.77		1.2			1.2			>0.99			2.8	2.6	0.74
Cardiac death	1.9	1.9	1	1.3	0.9	0.4	0	0.8	0.4		0.72	1.00		2.5	1.6	0.22
MI	2.8	2.4	1		4.1	2.9		2.8	1.8		0.33	0.04		4.6	5.7	0.30
STEMI	2.4	1.9	1	0	0.3		0	0.3			>0.99			0.8	0.5	0.35
NSTEMI	0.5	0.5	1	2.6	3.8		0.9	2.5			0.31			3.9	5.3	0.18
Stroke	0	0.5	1													
MACE	8.5	17.1	0.009	6.5	10.3	6.9	2.7	6.0	4.2		0.02	0.0009				
TVR	7.0	13.6	0.016		7.5			6.1			0.41			7.3	5.7	0.18
TLR	5.1	11.8	0.004		5.6	4.6		3.4	2.5		0.12	0.001		5.9	5.4	0.62
TVF	8.1	15.6	0.016		11.3			8.6			0.20					
TLF						6.8			4.2			0.001				
Definite or probable ST	1.4	1.4	1		0.6	1.10		1.1	0.29		0.73	0.004		2.2	2.6	0.66

BMS: Bare-metal stent; EUCATAX: Trial Comparing a Paclitaxel-Eluting Stent with Biodegradable Polymer Versus a Bare-Metal Stent; LEADERS: Limus Eluted From a Durable Versus Erodable Stent Coating; MACE: Major adverse cardiac event; MI: Myocardial infarction; NSTEMI: Non-ST-elevation myocardial infarction; PES: Paclitaxel-eluting stent; SPIRIT: Trial Comparing Everolimus-Eluting Stent with Paclitaxel-Eluted Stent; ST: Stent thrombosis; STEMI: ST-elevation myocardial infarction; TLF: Target lesion failure; TLR: Target lesion revascularization; TVF: Target vessel failure; TVR: Target vessel revascularization.

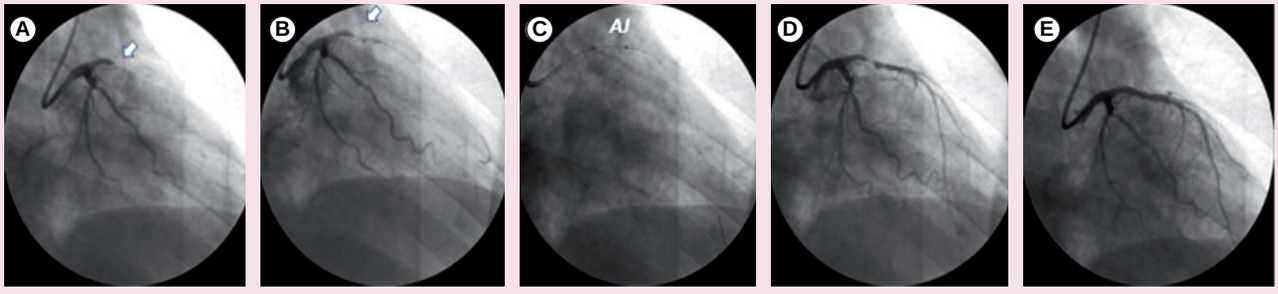

Figure 2. Patient with ST-elevation myocardial infarction. Patient with ST-elvation myocardial infarction with complete closure of the left anterior descending artery **(A & B)**, treated first with rheolytic thrombectomy **(C)** and stent placement **(D & E)**.

acetate], poly[n-butyl methacrylate] and poly[styrene-b-isobutylene-b-styrene]), which add an extra factor that influences local vascular responses. Each of these polymers provokes a distinctive inflammatory reaction in animals; for example, giant cell infiltration with progressive granulomatous and eosinophilic reaction [79,80]. These data support the perception that durable polymers in DES technology might provoke chronic inflammation and decreased safety/efficacy.

New technologies are arising with the introduction of biocompatible or biodegradable polymers (e.g., polylactide, polyglycolide, poly[L-lactic acid] and poly[glycolic acid]) using asymmetric abluminal coating. The purpose of these new designs is to avoid or minimize the undesirable side effects linked to durable polymers. Therefore, we now have positive randomized clinical trials with newer DES versus older generations. The industry is working hard to solve many of these problems. Results from trials using biodegradable and biocompatible polymers are encouraging, as testified by the approximate 1-year follow-up results from the Trial Comparing Everolimus-Eluting Stent with Paclitaxel-Eluted Stent (SPIRIT) II [81], SPIRIT III [82], SPIRIT IV [101], Limus Eluted From a Durable versus Erodable Stent Coating (LEADERS) [83], ABSORB [84] and the Trial Comparing a Paclitaxel-Eluting Stent with Biodegradable Polymer versus a Bare-Metal Stent (EUCATAX) [85] trials (Table 3). In EUCATAX, a new DES design using a dual-coating technology, a bioabsorbable polymer combined with a glycocalyx coating, showed significantly less late stent apposition compared with a BMS design, a unique finding that may be associated with the safety outcome of this device [85]. In fact, very late stent thrombosis was not seen with this new DES design.

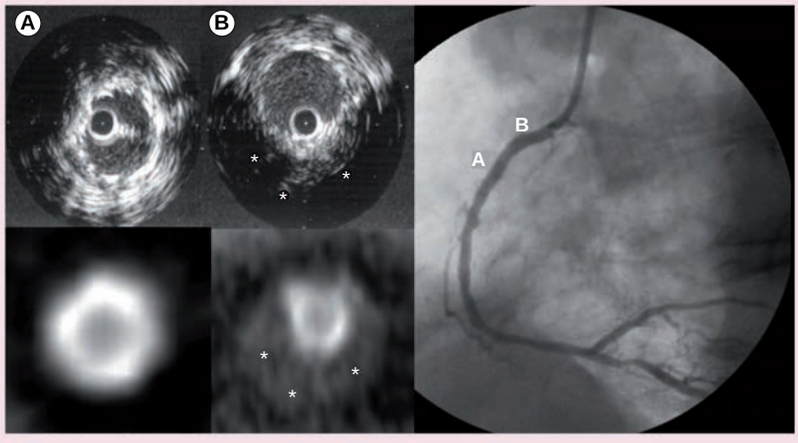

Figure 3. Patient with acute ST-elevation myocardial infarction. Patient with acute ST-elevation myocardial infarction with large hematomas in the proximal and mid portions of the right coronary sinus detected by intravascular ultrasound and computed tomographic angiography **(A & B)**; after stent placement, the hematomas was succesfully sealed (asterisks in **B**).

In addition, we are now using new drugs with different releasing profiles, which have significantly less endothelium dysfunction compared with first-generation DES [86]. Absence of endothelium dysfunction either with new drugs or by complete degradation of the polymer together with complete and fast release of the immunosuppressive agent have become key issues in stent design selection in patients with ACS.

Conversely, in patients with large thrombus burden, the use of rheolytic thrombectomy before DES deployment has been associated with low incidence of stent thrombosis at late follow-up [66]; therefore, its use in circumstances of large thrombus burden should be suggested. A recent randomized clinical trial with this device reports a significantly lower rate of major adverse events at 30 days and 6 months of follow-up [87]. It is reasonable that the use of aspiration devices before DES or BMS implantation should be recommended during PCI in STEMI

when a large thrombus burden is observed. As an example, in Figure 2 we show one patient with AMI who has a large thrombus burden in the RCA and left anterior descending arteries, in whom rheolytic thrombectomy was performed before implantation of a BMS (see Figure 2 legend for details).

■ New bare-metal stent designs

What are the potential solutions for the major limitations of BMS in patients with unstable coronary lesions (e.g., coronary restenosis)? We know that the vascular response to the healing process is the major advantage of BMS designs over DES, particularly in patients with unstable coronary lesions. Therefore, how can we improve the efficacy of the BMS without sacrificing safety?

In recent years, the industry and researchers have introduced in pre- and observational-clinical study BMS designs specially committed for patients with high-risk coronary thrombotic lesions. Recently, an observational study in patients with ACS with a semisynthetic coating of a BMS that mimics luminal endothelial cell glycocalyx (Camouflage®, Eucatech AG, Germany) has reported encouraging results in terms of safety outcome [88]. Camouflage coating provides a semisynthetic layer that serves as a model for a nonthrombogenic interface and promotes stent endothelialization. In fact, in this study, incidence of stent thrombosis was not found and an IVUS substudy during follow-up did not detect presence of late stent malapposition in STEMI patients. Furthermore, patients scheduled for an elective noncardiac surgery within the first month after stent deployment did not suffer any cardiac adverse events during hospitalization or in the following 30 days after PCI procedure. This group of patients, unable to take clopidogrel for longer than 1 or 2 weeks, are well known to be at high risk for catastrophic cardiac adverse events during the early hospitalization period [89,90].

In addition, a nitinol, self-expanding, tailored stent has been recently used to shield a vulnerable plaque [35]. No restenosis or stent malapposition was detected by IVUS and OCT restudies at follow-up. In Figure 3, we report a patient having an acute inferior MI with a coronary hematoma as a potential cause of subacute thrombosis. After successful implantation of a BMS, CTA and IVUS studies demonstrated complete sealing of the hematoma by the stent (asterisks in Figure 3B). In this patient, a balloon-expandable BMS sized one-to-one by IVUS was deployed, although this case is a good example of the potential use of self-expanding stents in unstable coronary lesions.

■ Alternative therapies to DES

Another potential alternative to DES technology is the use of drug-eluted balloon techniques, which have been successfully used to treat in-stent restenotic lesions [91], bifurcations and small vessels coronary artery disease, and they are currently being tested in randomized studies in patients with STEMI. Furthermore, with the use of this drug-eluting balloon, primary implantation of a stent after the treatment is not mandatory; therefore, some of the side effects associated with stent implantation in STEMI will not be present with this device.

We now have new tools beyond DES to reduce or prevent coronary restenosis using conventional BMS designs. During the last decade, we have observed the results from randomized clinical trials using systemic oral therapies after BMS implantation. All of these studies, although they did not include patients with STEMI, have systematically reported positive results using oral sirolimus, oral prednisone, oral thiazolidinediones or oral cilostazol [74,92–99]. Two of these studies have also reported sustained improvement at late follow-up [96,99].

None of the above therapies require long-term antiplatelet therapy. We have to recognize that besides patients who are nonresponsive to clopidogrel, there are other subgroups of patients with limited compliance to that therapy, whose characteristics include older age, upper and lower digestive tract bleeding, patients under oral anticoagulation therapy or with concomitant noncardiac illness [72,73]. Therefore, these patients are potential candidates for these alternative therapies.

Executive summary

- Percutaneous coronary interventions with bare-metal stent implantation have become the standard of care in patients with ST-elevation myocardial infarction during the first hours after symptom onset.
- Drug-eluting stents in randomized clinical trials demonstrated a significant reduction of angiographic restenosis; however, its role in lesions having large thrombus burden or lesions containing thrombus could be controversial.
- New drug-eluting stent designs with bioabsorbable polymers, dedicated bare-metal stents with antithrombotic coating layers, self-expanding nitinol stents or lately drug-eluting balloons were recently introduced and discussed in the article.

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Bibliography

Papers of special note have been highlighted as:
- of interest

1 Rodriguez A, Bernardi V, Fernandez M *et al.*: In-hospital and late results of coronary stents versus conventional balloon angioplasty in acute myocardial infarction (GRAMI trial). Gianturco–Roubin in Acute Myocardial Infarction. *Am. J. Cardiol.* 81, 1286–1291 (1998).

2 Antoniucci D, Santoro GM, Bolognese L, Valenti R, Trapani M, Fazzini PF: A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction: results from the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. *J. Am. Coll. Cardiol.* 31, 1234–1239 (1998).

3 Suryapranata H, van't Hof AW, Hoorntje JC, de Boer MJ, Zijlstra F: Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. *Circulation* 97, 2502–2505 (1998).

4 Grines CL, Cox DA, Stone GW *et al.*: Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N. Engl. J. Med.* 341, 1949–1956 (1999).

5 Saito S, Hosokawa G, Tanaka S, Nakamura S: Primary stent implantation is superior to balloon angioplasty in acute myocardial infarction: final results of the primary angioplasty versus stent implantation in acute myocardial infarction (PASTA) trial. PASTA Trial Investigators. *Catheter. Cardiovasc. Interv.* 48, 262–268 (1999).

6 Sousa JE, Costa MA, Abizaid AC *et al.*: Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 104, 2007–2011 (2001).

7 Morice MC, Serruys PW, Sousa JE *et al.*: A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N. Engl. J. Med.* 346, 1773–1780 (2002).

8 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.* 349, 1315–1323 (2003).

9 Grube E, Silber S, Hauptmann KE *et al.*: TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for *de novo* coronary lesions. *Circulation* 107, 38–42 (2003).

10 Colombo A, Drzewiecki J, Banning A *et al.*: Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 108, 788–794 (2003).

11 Stone GW, Ellis SG, Cox DA *et al.*: A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N. Engl. J. Med.* 350, 221–231 (2004).

12 Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW: A pooled analysis of data comparing sirolimus-eluting stents with bare-metal stents. *N. Engl. J. Med.* 356, 989–997 (2007).

13 Virmani R, Guagliumi G, Farb A *et al.*: Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109, 701–705 (2004).

14 Togni M, Windecker S, Cocchia R *et al.*: Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. *J. Am. Coll. Cardiol.* 46, 231–236 (2005).

15 Hong MK, Mintz GS, Lee CW *et al.*: Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation* 113, 414–419 (2006).

16 Kotani J, Awata M, Nanto S *et al.*: Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J. Am. Coll. Cardiol.* 47, 2108–2111 (2006).

17 Joner M, Finn AV, Farb A *et al.*: Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J. Am. Coll. Cardiol.* 48, 193–202 (2006).

18 Meier P, Zbinden R, Togni M *et al.*: Coronary collateral function long after drug-eluting stent implantation. *J. Am. Coll. Cardiol.* 49, 15–20 (2007).

19 Finn AV, Joner M, Nakazawa G *et al.*: Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* 115, 2435–2441 (2007).

20 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* 118, 1138–1145 (2008).

21 McFadden EP, Stabile E, Regar E *et al.*: Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 364, 1519–1521 (2004).

22 Iakovou I, Schmidt T, Bonizzoni E *et al.*: Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 293, 2126–2130 (2005).

23 Spertus JA, Kettelkamp R, Vance C *et al.*: Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 113, 2803–2809 (2006).

24 Rodriguez AE, Mieres J, Fernandez-Pereira C *et al.*: Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J. Am. Coll. Cardiol.* 47, 205–207 (2006).

25 Rodriguez AE, Rodriguez-Granillo GA, Palacios IF: Late stent thrombosis: the Damocle's sword of drug-eluting stents? *EuroIntervention* 2, 512–517 (2007).

26 Daemen J, Wenaweser P, Tsuchida K *et al.*: Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 369, 667–678 (2007).

27 Kolodgie FD, Virmani R, Burke AP *et al.*: Pathologic assessment of the vulnerable human coronary plaque. *Heart* 90, 1385–1391 (2004).

28 Virmani R, Burke AP, Farb A, Kolodgie FD: Pathology of the vulnerable plaque. *J. Am. Coll. Cardiol.* 47, C13–C18 (2006).

29 Kolodgie FD, Burke AP, Farb A *et al.*: The thin-cap fibroatheroma: a type of vulnerable plaque: the major precursor lesion to acute coronary syndromes. *Curr. Opin. Cardiol.* 16, 285–292 (2001).

30 Finn AV, Nakazawa G, Joner M *et al.*: Vascular responses to drug-eluting stents: importance of delayed healing. *Arterioscler. Thromb. Vasc. Biol.* 27, 1500–1510 (2007).

31 Hofma SH, van der Giessen WJ, van Dalen BM *et al.*: Indication of long-term endothelial dysfunction after sirolimus-eluting stent implantation. *Eur. Heart J.* 27, 166–170 (2006).

32 Fuke S, Maekawa K, Kawamoto K *et al.*: Impaired endothelial vasomotor function after sirolimus-eluting stent implantation. *Circ. J.* 71, 220–225 (2007).

33 Jabs A, Gobel S, Wenzel P *et al.*: Sirolimus-induced vascular dysfunction. Increased mitochondrial and nicotinamide adenosine dinucleotide phosphate oxidase-dependent superoxide production and decreased vascular nitric oxide formation. *J. Am. Coll. Cardiol.* 51, 2130–2138 (2008).

34 Waxman S, Ishibashi F, Muller JE: Detection and treatment of vulnerable plaques and vulnerable patients: novel approaches to prevention of coronary events. *Circulation* 114, 2390–2411 (2006).

35 Garcia-Garcia HM, Gonzalo N, Granada JF, Regar E, Serruys PW: Diagnosis and treatment of coronary vulnerable plaques. *Expert Rev. Cardiovasc. Ther.* 6, 209–222 (2008).

36 Rodriguez-Granillo GA, Regar E, Schaar JA, Serruys PW: New insights towards catheter-based identification of vulnerable plaque. *Rev. Esp. Cardiol.* 58, 1197–1206 (2005).

37 Sawada T, Shite J, Garcia-Garcia HM *et al.*: Feasibility of combined use of intravascular ultrasound radiofrequency data analysis and optical coherence tomography for detecting thin-cap fibroatheroma. *Eur. Heart J.* 29, 1136–1146 (2008).

38 Gonzalo N, Garcia-Garcia HM, Regar E *et al.*: *In vivo* assessment of high-risk coronary plaques at bifurcations with combined intravascular ultrasound and optical coherence tomography. *JACC Cardiovasc. Imaging* 2, 473–482 (2009).

39 Caplan JD, Waxman S, Nesto RW, Muller JE: Near-infrared spectroscopy for the detection of vulnerable coronary artery plaques. *J. Am. Coll. Cardiol.* 47, C92–C96 (2006).

40 Gardner CM, Tan H, Hull EL *et al.*: Detection of lipid core coronary plaques in autopsy specimens with a novel catheter-based near-infrared spectroscopy system. *JACC Cardiovasc. Imaging* 1, 638–648 (2008).

41 Goldstein JA: Coronary plaque characterization by computed tomographic angiography: present promise and future hope. *JACC Cardiovasc. Imaging* 2, 161–163 (2009).

42 Braunwald E: Noninvasive detection of vulnerable coronary plaques: locking the barn door before the horse is stolen. *J. Am. Coll. Cardiol.* 54, 58–59 (2009).

43 Rodriguez-Granillo GA: Non-invasive assessment of vulnerable plaque. *Expert Opin. Med. Diagn.* 3, 53–66 (2009).

44 Valgimigli M, Percoco G, Malagutti P *et al.*: Tirofiban and sirolimus-eluting stent vs abciximab and bare-metal stent for acute myocardial infarction: a randomized trial. *JAMA* 293, 2109–2117 (2005).

45 Spaulding C, Henry P, Teiger E *et al.*: Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N. Engl. J. Med.* 355, 1093–1104 (2006).

46 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.* 49, 1924–1930 (2007).

47 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.* 28, 2706–2713 (2007).

48 Pasceri V, Patti G, Speciale G, Pristipino C, Richichi G, Di Sciascio G: Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am. Heart J.* 153, 749–754 (2007).

49 Di Lorenzo E, Sauro R, Varricchio A *et al.*: Benefits of drug-eluting stents as compared to bare-metal stent in ST-segment elevation myocardial infarction: four year results of the Paclitaxel or Sirolimus-Eluting Stent vs Bare-Metal Stent in Primary Angioplasty (PASEO) randomized trial. *Am. Heart J.* 158, E43–E50 (2009).

50 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* 299, 1788–1799 (2008).

51 Pfisterer M, Brunner-La Rocca HP, Buser PT *et al.*: Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J. Am. Coll. Cardiol.* 48, 2584–2591 (2006).

52 Norhammar A, Lagerqvist B, Saleh N: Long-term mortality after PCI in patients with diabetes mellitus: results from the Swedish Coronary Angiography and Angioplasty Registry. *EuroIntervention* 5, 891–897 (2010).

53 Jensen LO, Tilsted HH, Thayssen P *et al.*: Paclitaxel and sirolimus-eluting stents versus bare-metal stents: long-term risk of stent thrombosis and other outcomes. From the Western Denmark Heart Registry. *EuroIntervention* 5, 898–905 (2010).

54 Garg S, Eisenberg MJ: Drug-eluting stents more dollars than sense? *JACC Cardiovasc. Interv.* 2, 1188–1189 (2009).

55 Caixeta A, Leon MB, Lansky AJ *et al.*: 5-year clinical outcomes after sirolimus-eluting stent implantation insights from a patient-level pooled analysis of 4 randomized trials comparing sirolimus-eluting stents with bare-metal stents. *J. Am. Coll. Cardiol.* 54, 894–902 (2009).

▪ **Along with references** [65,67]**, this article highlights the relationship between drug-eluting stents (DES) and stent thrombosis in high-risk subgroups such as patients with diabetes and ST-segment elevation myocardial infarction (STEMI).**

56 Moreno PR, Fuster V: New aspects in the pathogenesis of diabetic atherothrombosis. *J. Am. Coll. Cardiol.* 44, 2293–2300 (2004).

57 Moreno PR, Murcia AM, Palacios IF *et al.*: Coronary composition and macrophage infiltration in atherectomy specimens from patients with diabetes mellitus. *Circulation* 102, 2180–2184 (2000).

58 Burke AP, Kolodgie FD, Zieske A *et al.*: Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study. *Arterioscler. Thromb. Vasc. Biol.* 24, 1266–1271 (2004).

59 Rodriguez AE: Left main stenting: long term outcome and comparison among DES and BMS. Presented at: *Cardiovascular Research Technologies (CRT) Meeting 2010.* Washington, DC, USA, 21–23 February 2010.

60 Rodriguez AE, Fernandez M, Santaera O *et al.*: Coronary stenting in patients undergoing percutaneous transluminal coronary angioplasty during acute myocardial infarction. *Am. J. Cardiol.* 77, 685–689 (1996).

61 Laarman GJ, Suttorp MJ, Dirksen MT *et al.*: Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. *N. Engl. J. Med.* 355, 1105–1113 (2006).

62 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.* 51, 618–626 (2008).

63 Clemmensen P: Long term outcome of DES and BMS implantation in patients with ST-elevation MI: 3 years follow up of the randomized DEDICATION trial. Presented at: *American College of Cardiology 59th Annual Scientific Session.* Atlanta, GA, USA, 14–16 March 2010.

64 Vlaar PJ, de Smet BJ, Zijlstra F: DES or BMS in acute myocardial infarction? *Eur. Heart J.* 28, 2693–2694 (2007).

65 Steg PG, Fox KA, Eagle KA *et al.*: 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.* 30, 321–329 (2009).

▪ **Along with references** [55,67]**, this article highlights the relationship between DES and stent thrombosis in high-risk subgroups such as patients with diabetes and STEMI.**

66 Cook S, Wenaweser P, Togni M *et al.*: Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 115, 2426–2434 (2007).

▪ **First article to demonstrate the relationship between late-stent malapposition and stent thrombosis.**

67 Kukreja N, Onuma Y, Garcia-Garcia HM, Daemen J, van Domburg R, Serruys PW: The risk of stent thrombosis in patients with acute coronary syndromes treated with bare-metal and drug-eluting stents. *JACC Cardiovasc. Interv.* 2, 534–541 (2009).

▪ **Along with references** [55,65]**, this article highlights the relationship between DES and stent thrombosis in high-risk subgroups such as patients with diabetes and STEMI.**

68 Garro N, Capodanno D, Cammalleri V, Tamburino C: Very late thrombosis in acute myocardial infarction: drug-eluting versus uncoated stents. *EuroIntervention* 4, 324–330 (2008).

69 Daemen J, Tanimoto S, Garcia-Garcia 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.* 99, 1027–1032 (2007).

70 Sianos G, Papafaklis MI, Daemen J *et al.*: Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J. Am. Coll. Cardiol.* 50, 573–583 (2007).

71 Gonzalo N, Barlis P, Serruys PW *et al.*: Incomplete stent apposition and delayed tissue coverage are more frequent in drug-eluting stents implanted during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction than in drug-eluting stents implanted for stable/unstable angina: insights from optical coherence tomography. *JACC Cardiovasc. Interv.* 2, 445–452 (2009).

72 Gori AM, Marcucci R, Migliorini A *et al.*: Incidence and clinical impact of dual nonresponsiveness to aspirin and clopidogrel in patients with drug-eluting stents. *J. Am. Coll. Cardiol.* 52, 734–739 (2008).

73 Bhatt DL, Fox KA, Hacke W *et al.*: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N. Engl. J. Med.* 354, 1706–1717 (2006).

74 Rodriguez AE, Granada JF, Rodriguez-Alemparte M *et al.*: Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the Prospective, Randomized Oral Rapamycin in Argentina (ORAR II) study. *J. Am. Coll. Cardiol.* 47, 1522–1529 (2006).

75 Leon MB, Kandzari DE, Eisenstein EL *et al.*: Late safety, efficacy, and cost–effectiveness of a zotarolimus-eluting stent compared with a paclitaxel-eluting stent in patients with *de novo* coronary lesions 2-year follow-up from the ENDEAVOR IV Trial (Randomized, Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System versus the Taxus Paclitaxel-Eluting Coronary Stent System in *De Novo* Native Coronary Artery Lesions). *JACC Cardiovasc. Interv.* 2, 1208–1218 (2009).

76 Eisenstein EL, Leon MB, Kandzari DE *et al.*: Long-term clinical and economic analysis of the Endeavor zotarolimus-eluting stent versus the Cypher sirolimus-eluting stent 3-year results from the ENDEAVOR III trial (Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System versus the Cypher Sirolimus-Eluting Coronary Stent System in *De novo* Native Coronary Artery Lesions). *JACC Cardiovasc. Interv.* 2, 1199–1207 (2009).

77 Jimenez-Quevedo P, Sabate M, Angiolillo DJ *et al.*: Vascular effects of sirolimus-eluting versus bare-metal stents in diabetic patients: three-dimensional ultrasound results of the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial. *J. Am. Coll. Cardiol.* 47, 2172–2179 (2006).

78 Guagliumi G, Sirbu V: Optical coherence tomography: high resolution intravascular imaging to evaluate vascular healing after coronary stenting. *Catheter. Cardiovasc. Interv.* 72, 237–247 (2008).

79 Finn AV, Kolodgie FD, Harnek J *et al.*: Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 112, 270–278 (2005).

80 Finn AV, Nakazawa G, Kolodgie FD, Virmani R: Temporal course of neointimal formation after drug-eluting stent placement: is our understanding of restenosis changing? *JACC Cardiovasc. Interv.* 2, 300–302 (2009).

81 Serruys PW, Ruygrok P, Neuzner J *et al.*: A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *EuroIntervention* 2, 286–294 (2006).

82 Stone GW, Midei M, Newman W *et al.*: Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA* 299, 1903–1913 (2008).

83 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 randomised non-inferiority trial. *Lancet* 372, 1163–1173 (2008).

84 Ormiston JA, Serruys PW, Regar E *et al.*: A bioabsorbable everolimus-eluting coronary stent system for patients with single *de-novo* coronary artery lesions (ABSORB): a prospective open-label trial. *Lancet* 371, 899–907 (2008).

85 Rodriguez AE, Vigo FC, Delacasa A *et al.*: Comparison of a paclitaxel-eluting stent with biodegradable polymer and glycolix coating versus bare-metal stent design: first presentation of 9 months clinical and angiographic outcome of the randomized, multicenter and controlled EUCATAX Trial. Presented at: *American College of Cardiology 59th Annual Scientific Session.* Atlanta, GA, USA, 14–16 March 2010.

86 Hamilos MI, Ostojic M, Beleslin B *et al.*: Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. *J. Am. Coll. Cardiol.* 51, 2123–2129 (2008).

87 Migliorini A, Stabile A, Rodriguez A *et al.*: Randomized comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction: the JESTENT trial. *J. Am. Coll. Cardiol.* (2010) (In Press).

88 Perez G, Rodriguez-Granillo AM, Mieres J *et al.*: New coating stent design for patients with high-risk coronary lesions for thrombotic events: early and long-term results of the Camouflage registry. *J. Invasive Cardiol.* 21, 378–382 (2009).

89 Kaluza GL, Joseph J, Lee JR, Raizner ME, Raizner AE: Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J. Am. Coll. Cardiol.* 35, 1288–1294 (2000).

90 Rhee SJ, Yun KH, Lee SR *et al.*: Drug-eluting stent thrombosis during perioperative period. *Int. Heart J.* 49, 135–142 (2008).

91 Scheller B, Hehrlein C, Bocksch W *et al.*: Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N. Engl. J. Med.* 355, 2113–2124 (2006).

92 Versaci F, Gaspardone A, Tomai F *et al.*: Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS study). *J. Am. Coll. Cardiol.* 40, 1935–1942 (2002).

93 Ribichini F, Tomai F, Ferrero V *et al.*: Immunosuppressive oral prednisone after percutaneous interventions in patients with multi-vessel coronary artery disease. The IMPRESS-2/MVD study. *EuroIntervention* 1, 173–180 (2005).

94 Douglas JS Jr, Holmes DR Jr, Kereiakes DJ *et al.*: Coronary stent restenosis in patients treated with cilostazol. *Circulation* 112, 2826–2832 (2005).

95 Brito FS, Jr., Rosa WC, Arruda JA, Tedesco H, Pestana JO, Lima VC: Efficacy and safety of oral sirolimus to inhibit in-stent intimal hyperplasia. *Catheter. Cardiovasc. Interv.* 64, 413–418 (2005).

96 Rodriguez AE, Maree A, Tarragona S *et al.*: Percutaneous coronary intervention with oral sirolimus and bare-metal stents has comparable safety and efficacy to treatment with drug-eluting stents, but with significant cost saving: long-term follow-up results from the randomised, controlled ORAR III (Oral Rapamycin in Argentina) study. *EuroIntervention* 5, 255–264 (2009).

97 Jeong YH, Lee SW, Choi BR *et al.*: Randomized comparison of adjunctive cilostazol versus high maintenance dose clopidogrel in patients with high post-treatment platelet reactivity: results of the ACCEL-RESISTANCE (Adjunctive Cilostazol Versus High Maintenance Dose Clopidogrel in Patients With Clopidogrel Resistance) randomized study. *J. Am. Coll. Cardiol.* 53, 1101–1109 (2009).

98 Stojkovic S, Ostojic M, Nedeljkovic M *et al.*: Systemic rapamycin without loading dose for restenosis prevention after coronary bare-metal stent implantation. *Catheter. Cardiovasc. Interv.* 75, 317–325 (2010).

99 Cernigliaro C, Sansa M, Vitrella G *et al.*: Preventing restenosis after implantation of bare stents with oral rapamycin: a randomized angiographic and intravascular ultrasound study with a 5-year clinical follow-up. *Cardiology* 115, 77–86 (2010).

■ Website

101 Abbott's XIENCE V® Superior to TAXUS® in Key Safety and Efficacy Measures in SPIRIT IV Trial, 23 September 2009 www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0774.htm