World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/1949-8462office
wjc@wjgnet.com
doi:10.4330/wjc.v3.i3.84

World J Cardiol 2011 March 26; 3(3): 84-92
ISSN 1949-8462 (online)

REVIEW

Advantages and disadvantages of biodegradable platforms in drug eluting stents

Agustina Rodriguez-Granillo, Bibiana Rubilar, Gaston Rodriguez-Granillo, Alfredo E Rodriguez

Agustina Rodriguez-Granillo, Center for Advanced Biotechnology and Medicine, Rutgers University, New Jersey, NJ 08854, United States
Bibiana Rubilar, Staff Cardiac Unit, Otamendi Hospital, Buenos Aires C1024AAA, Argentina
Gaston Rodriguez-Granillo, Intravascular Imaging, Cardiac Unit, Otamendi Hospital, Buenos Aires C1024AAA, Argentina
Alfredo E Rodriguez, Cardiac Unit, Otamendi Hospital, Cardiovascular Research Center (CECI), Buenos Aires C1024AAA, Argentina
Correspondence to: Alfredo E Rodriguez, MD, PhD, FACC, FSCAI, Head, Director, Cardiac Unit, Otamendi Hospital, Cardiovascular Research Center (CECI), Callao 1441 4B Capital Federal, Buenos Aires C1024AAA,
Argentina. rodrigueza@sanatorio-otamendi.com.ar
Telephone: +54-11-49648721 Fax: +54-11-49629012
Received: January 8, 2011 Revised: February 14, 2011
Accepted: February 21, 2011
Published online: March 26, 2011

Abstract

Coronary angioplasty with drug-eluting stent (DES) implantation is currently the most common stent procedure worldwide. Since the introduction of DES, coronary restenosis as well as the incidence of target vessel and target lesion revascularization have been significantly reduced. However, the incidence of very late stent thrombosis beyond the first year after stent deployment has more commonly been linked to DES than to bare-metal stent (BMS) implantation. Several factors have been associated with very late stent thrombosis after DES implantation, such as delayed healing, inflammation, stent mal-apposition and endothelial dysfunction. Some of these adverse events were associated with the presence of durable polymers, which were essential to allow the elution of the immunosuppressive drug in the first DES designs. The introduction of erodable polymers in DES technology has provided the potential to complete the degradation of the polymer simultaneously or immediately after the release of the immunosuppressive drug, after which a BMS remains in place. Several DES designs with biodegradable (BIO) polymers have been introduced in preclinical and clinical studies, including randomized trials. In this review, we analyze the clinical results from 6 observational and randomized studies with BIO polymers and discuss advantages and disadvantages of this new technology.

Key words: Polymers; Drug eluting stents; Biodegradable polymers ; Stents; Thrombosis; Restenosis

Peer reviewers: Hiroki Teragawa, MD, PhD, Department of Cadiovascular Medicine, Hiroshima General Hospital of West Japan Railway Company, 3-1-36 Futabanosato, Higashi-ku, Hiroshima 732-0052, Japan; Tommaso Gori, MD, PhD, II Medizinische Klinik, Universitätsmedizin der Johannes Gutenberg Universitats Mainz, 55131 Mainz, Germany; Masamichi Takano, MD, PhD, Cardiovascular Center, Chiba-Hokusoh Hospital, Nippon Medical School, 1715 Kamakari, Imba, Chiba, 270-1694, Japan

Rodriguez-Granillo A, Rubilar B, Rodriguez-Granillo G, Rodriguez AE. Advantages and disadvantages of biodegradable platforms in drug eluting stents. *World J Cardiol* 2011; 3(3): 84-92 Available from: URL: http://www.wjgnet.com/1949-8462/full/v3/i3/84.htm DOI: http://dx.doi.org/10.4330/wjc.v3.i3.84

INTRODUCTION

A significant reduction in coronary restenosis rates has been observed with the introduction of drug-eluting stent (DES) technology during percutaneous coronary interventions (PCI)[1-6]. During these years, we have also learned that some adverse effects, although rarely present, are more frequently associated with DES implantation[7-14]; some of them can be linked to durable polymers, which were continually present in the first DES designs[1-6]. Delayed healing, endothelial dysfunction, chronic arterial wall inflammation and late-acquired stent mal-apposition are more frequently linked with DES im-

plantation[9-15]. All of these can increase the incidence of very late stent thrombosis that, although an uncommon event, was more frequently reported after DES implantation[16-21]. Delayed loss of anti-restenotic efficacy was also reported with the first DES designs[22,23]. Chronic arterial wall inflammation and endothelial dysfunction may be associated with the increased rate of target vessel revascularization (TVR) at a late stage, which has been found particularly in patients with complex lesions including those with diabetes[24,25]. All of the above underscore the importance of this topic, especially after reports of increased rate of endothelial dysfunction after DES implantation as compared with bare-metal stent (BMS) implantation.

FIRST DES DESIGNS

Three main components were necessary to achieve a stable release of the drug in the first DES generation: the stent platform to scaffold the vessel, the polymer to deliver the immunosuppressive agent and the drug to inhibit neointimal growth.

Initially, sirolimus-eluting stents (SES; Cypher™, Cordis Co., Warren, NJ, USA) and paclitaxel-eluting stents (PES; Taxus™, Boston Scientific Co., Natick, MA, USA) were designed using permanent polymers such as poly(ethylene-co-vinyl acetate), poly(n-butyl methacrylate) and poly(styrene-b-isobutylene-b-styrene), which allowed controlled elution of the immunosuppressive agent. The SES design consists of a stainless steel platform coated with a permanent polymer containing sirolimus 140 μg/cm^2, 80% of which is released within 30 d. The PES design is also composed of a stainless steel platform with a permanent polymer coating combined with 1 μg/mm^2 paclitaxel; 10% of the paclitaxel is released within 2 wk after stent deployment, although 90% of it remains in the polymer forever[24,26].

The presence of permanent polymers in the vessel arterial wall adds an additional factor that influences local responses and may alter processes involved in neointimal formation. Each polymer provokes a distinctive inflammatory response in animals, such as giant cell infiltration around the stent struts, and a progressive granulomatous and eosinophilic reaction[23,27], which increase beyond the first year. These data support the perception that durable polymers in DES technology may provoke chronic inflammation and decreased efficacy.

BIODEGRADABLE POLYMERS IN DES TECHNOLOGY

The use of biodegradable (BIO) polymers, as opposed to durable polymers, in coronary stent technology has the advantages of a complete elution of drugs and a reduced inflammatory response, with the potential for decreasing the risk of late complications such as stent strut uncovering, mal-apposition, endothelial dysfunction and thrombosis[5,7,9,10,28,29]. BIO polymers allow the complete release and elution of the immunosuppressive agent after degradation of the polymer[26,29]. Therefore, long-term antiplatelet therapy would not be required after the polymer completely disappeared. The most common BIO polymers are composed of polylactic acid (PLA), polyglycolide and poly(D,L-lactic-co-glycolic acid) (PLGA), which are completely metabolized into the body (breaking down into monomers, water and carbon dioxide) after fulfilling their purpose.

Several new stents with fully BIO polymers have been introduced using a variety of anti-proliferative agents such as sirolimus, tacrolimus, biolimus and paclitaxel. The safety and efficacy of these devices have been assessed clinically in first in man (FIM) and observational studies[30-32]. For example, in the Paclitaxel In Stent Controlled Elution Study, the pharmacokinetics of the DES and not dose of the immunosuppressive agent appears to be associated with neointimal suppression and clinical outcome[30]. However, an excess of late loss with a high rate of clinical angiographic restenosis and also a lack of reduction in stent thrombosis were reported in many of these FIM studies. A high inflammatory reaction due to major particle debris as a result of coating degradation, which was not simultaneous with drug release, was a major limitation for many of the first DES designs with BIO polymers. Therefore, to the best of our knowledge, only 6 DES with erodable polymers have randomized clinical data with enough patients to justify their introduction in clinical practice.

In the following paragraphs we will review and summarize the main findings from published randomized data of the Limus Eluted from a Durable *vs* Erodable Stent Coating (LEADERS)[28], NOBORI[33,34], Individualized Drug Eluting Stent System to Abrogate Restenosis (ISAR)-TEST-3[35] and TEST-4[36,37] with sirolimus (rapamycin), PAINT (percutaneous intervention with BIO-polymer based paclitaxel-eluting or sirolimus-eluting *vs* bare stents for *de novo* coronary lesions)[38] and EUCATAX[39] trials. Study and stent design of each trial is described in Table 1.

LEADERS TRIAL

The LEADERS trial[28] is the largest randomized trial with BIO polymer-coated stents. The study compared a PLA polymer loaded with Biolimus (Biolimus-eluting stent; BioMatrix Flex, Biosensors Inc, Newport Beach, CA, USA) *vs* a Cypher platform (SES). The BIO polymer was applied to the stent's abluminal surface only. After an initial burst of 40% of drug elution, complete drug release and polymer degradation was achieved over a period of 6 to 9 mo.

The LEADERS trial enrolled 1707 randomized patients, 807 included in the BIO polymer (BioMatrix Flex) and 850 in the durable polymer (Cypher) DES arms. The study included a large proportion of patients with acute coronary syndromes (55%) including ST elevation myocardial infarction (STEMI), multiple vessel disease (24%), previous PCI (36%) and vessel size < 2.75 mm (68%). At 9 mo of follow-up, all clinical endpoints met the criteria

Table 1 Comparison between published trials of biodegradable eluting stents

Name	Polymer	Stent design	Drug	Drug per stent length (μg/mm^2)	Polymer degradation	Drug release
ISAR-TEST-3[35]	PLA	316L stainless steel microporus stent	Sirolimus	4.8	6-9 wk	28 d (95%)
ISAR TEST-4[36]	PLA	316L stainless-steel microporus stent	Sirolimus	4.8	6-9 wk	28 d (95%)
NOBORI 1[34]	PLA	Stainless-steel S-stent	Biolimus	15.6	9-12 mo	Two phases: immediately after stent implantation; sustained drug release over 9-12 mo
NOBORI CORE[33]	PLA	Stainless-steel S-stent	Biolimus	15.6	9-12 mo	Two phases: immediately after stent implantation; sustained drug release over 9-12 mo
LEADERS[28]	PLA	Flexible stainless- steel stent	Biolimus	15.6	6-9 mo	6-9 mo
PAINT[38]	PLA+ PLGA	316L stainless metallic platform	Paclitaxel and Sirolimus	6.4 (PES) 6.6 (SES)	7 mo	9-11 d (50%) 38 d (90%) 48 d (100%)
EUCATAX[39]	PLGA	Stainless steel open cell with glycocalix layer	Paclitaxel	11 to 43	6-8 wk	6-8 wk

PLA: Polylactic acid; PLGA: Polylactic-co-glycolic acid; PES: Paclitaxel-eluting stent; SES: Sirolimus-eluting stent; ISAR: Individualized Drug Eluting Stent System to Abrogate Restenosis; LEADERS: Limus Eluted from a Durable *vs* Erodable Stent Coating.

of non-inferiority for the BioMatrix-Flex compared to Cypher, including the amount of late loss in the follow-up angiogram.

The incidence of all definitions of stent thrombosis was also similar between both DES designs (3.6% in BioMatrix-Flex and 3.3% in Cypher), although percent of uncovered (3.6% *vs* 39% in BioMatrix-Flex and Cypher, respectively, $P = 0.005$) or mal-apposed (0.3% *vs* 6.7% in BioMatrix-Flex and Cypher, respectively, $P = 0.04$) stent struts were significant higher in the Cypher stent arm. At 2 years of follow-up, the LEADERS trial also showed a superior outcome with BioMatrix in patients with STEMI as testified by the rates of major adverse cardiovascular events (MACCE; 8.1% for BioMatrix-Flex *vs* 19.3% for Cypher, $P < 0.01$); the incidence of stent thrombosis in this cohort of patients was significantly lower with BioMatrix-Flex compared with Cypher (2.6% *vs* 8.4%, respectively, $P < 0.05$).

In the short-term follow-up, there was a high incidence of non-STEMI in patients allocated to the BioMatrix-Flex polymer (5.4%), and a high incidence of stent thrombosis in patients with STEMI allocated to the SES arm.

NOBORI TRIAL

The Nobori stent (Terumo Co., Tokyo, Japan) uses a similar drug-polymer combination (Biolimus/PLA) as the one in BioMatrix in the LEADERS trial. In this trial[33,34], 243 patients were randomized in a 2:1 ratio between Biolimus with BIO polymer stents (Nobori) and paclitaxel with durable polymer stents (Taxus).

At 9 mo of follow-up, the use of a DES with BIO polymer compared with the Taxus Liberte DES significantly reduced the amount of late loss and angiographic restenosis. Furthermore, although not powered to detect clinical differences, the incidence of target lesion revascularization (TLR) and TVR were also significantly better with the Nobori stent design. Remarkably, stent thrombosis was not seen in the erodable polymer arm compared with 4.4% in the Taxus Liberte arm. There was a small sample size, a short-term outcome and a high rate of stent thrombosis in the Taxus Liberte arm.

ISAR-TEST-3 AND -TEST-4 TRIALS

ISAR-TEST-3 trial

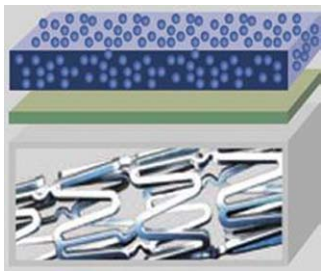
The ISAR-TEST-3 trial[35] enrolled 605 patients randomized to a BIO polymer stent loaded with sirolimus, a sirolimus polymer-free stent and a sirolimus with permanent polymer stent (Cypher; Cordis, Florida, USA). The BIO polymer was completely absorbed within 6 to 9 wk after stent deployment, whereas 100% of sirolimus was released within the first 30 d. The main finding of this study was that the BIO polymer stent was not inferior to the Cypher stent in safety and efficacy, whereas the polymer-free stent was inferior in terms of efficacy to the other 2 DES designs.

This study had a small sample size, a short-term outcome and, in this DES stent design, the BIO polymer remains in place after the drug is completely eluted, therefore inflammatory reactions by the polymer itself cannot be excluded.

ISAR-TEST-4 trial

The ISAR-TEST-4 trial[36] enrolled 2603 patients randomized to a BIO polymer DES (1299) or a permanent polymer DES (1304). In the latest group, 652 patients were treated with a Cypher stent and 652 with Xience V (Abbott Vascular, Abbott Park, IL, USA). At 1 year of follow-up, there were no differences in angiographic and clinical endpoints among patients treated with a BIO or permanent polymer, and the stent clearly met the non-inferiority test in both cases.

Two years follow-up of this trial was recently pre-



Drug content 0.25 μg/mm^2
Drug release: within 8-10 wk 100%
PLGA matrix degradation: 100%
Base layer Camouflage® full biological, athrombogenic coating; is a mimicry of the natural arterial glycocalix

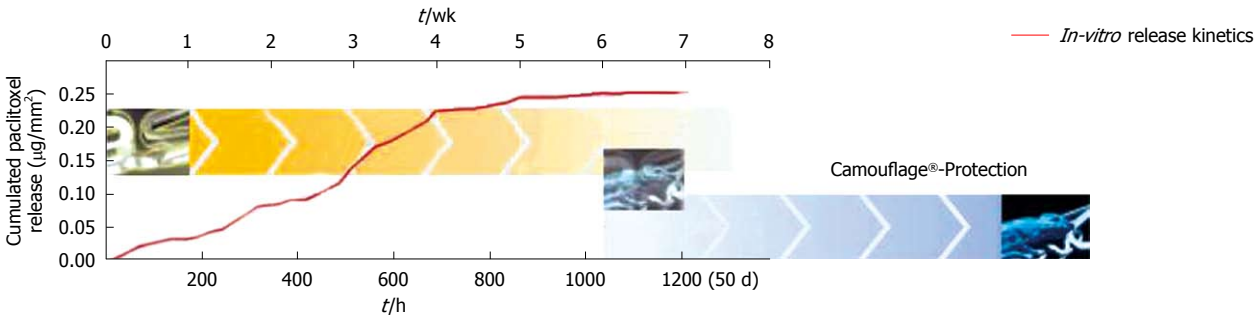


Figure 1 EUCATAX design and characteristics. PLGA: Poly(D,L-lactic-co-glycolic acid).

sented[37], and a sustained equivalence in the incidence of safety/efficacy end points between BIO and permanent polymer DES designs was seen. The incidence of stent thrombosis was similar in both study arms.

This study had a short-term outcome and the same concerns regarding the BIO polymer DES design described above for ISAR-TEST-3.

PAINT TRIAL

The PAINT trial[38] compared 2 DES with the same BIO polymer but with a different immunosuppressive drug (paclitaxel or sirolimus) *vs* a BMS design; 274 patients were randomly assigned to paclitaxel with BIO polymer (n = 111), sirolimus with BIO polymer (n = 106) and BMS (n = 57). All stents had the same laser cut stainless steel platform. Both paclitaxel and sirolimus were released in approximately 48 d, whereas complete polymer degradation occurred only after 7 mo.

Both DES designs had less late loss and TVR compared with the BMS, whereas SES had a lower late loss but similar 1-year clinical outcome compared with PES. All-cause death, MI and stent thrombosis were similar in the 3 groups.

The study had a small sample size, short period of follow-up, greater amount of in stent late loss with both BIO polymers in comparison with historical studies with the same drugs but a permanent polymer. Although the study did not show any significant differences in stent thrombosis rate among the different groups, this event occurred in 1.9% of each DES design compared with zero in the BMS arm. Finally, taking into consideration that release of the drug and degradation of the polymer was not simultaneous, similar concerns with this stent design can be applied to those described in the ISAR-TEST studies.

EUCATAX TRIAL

The rationale and purpose of the EUCATAX trial[39] was to compare the efficacy and safety of a new PES dual coated with a BIO polymer and glycocalyx against an equivalent BMS (Eucatech AG, Reinhelfeden; Germany). A FIM study was previously conducted[40].

The PES is a stainless steel open cell (strut thickness 85 μm) modular design with 3 connecting fins *per modulo*. The double coating includes a BIO polymer as the platform for paclitaxel elution and a glycocalyx to increase hemocompatibility. The glycocalyx layer is a symmetric coating that uses camouflage nanotechnology. The BIO polymer is PLGA, which forms an asymmetric coating with a thickness of 2.5 μm on the luminal side and 5 μm on the abluminal side. Paclitaxel is loaded into the polymer, at a concentration of 11 to 43 μg depending on the stent length. The camouflage nanocoating[41] is coated with hemo-heparin, which is a polymer-analogous modified heparin that lacks an active anticoagulation effect due to removal of the sulfate groups. On top of this hemo-heparin coat, the bio-absorbable polyester polymer PLGA serves as the carrier of the paclitaxel. In this stent design, degradation of the polymer occurred simultaneously with the elution of the drug at 6 to 8 wk after deployment. Therefore, according to the manufacturers, neither the drug nor the polymer remained in place (Figure 1).

The study included 422 patients (9.1% of those screened) and randomized 211 patients to the PES arm and 211 to the BMS arm (Figure 2). The population included diabetes in 23.5%, a reference vessel diameter size < 2.75 mm in 60%, multi-vessel disease in 60%, and acute coronary syndrome in 60%.

Cumulative clinical events at 18.3 ± 7.3 mo are shown in Figure 3. Cumulative cardiac events such as death,

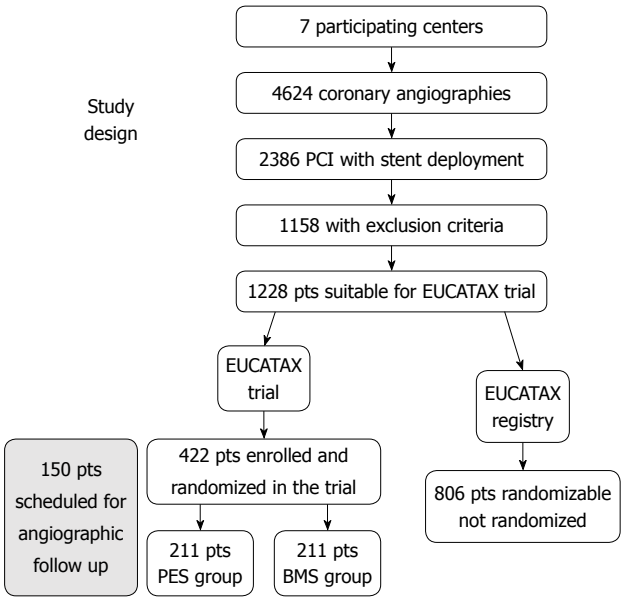


Figure 2 EUCATAX randomized trial design. Modified form Rodriguez *et al*[39]. Pts: Patients; PCI: Percutaneous coronary interventions; PES: Paclitaxel eluting stent; BMS: Bare-metal stent.

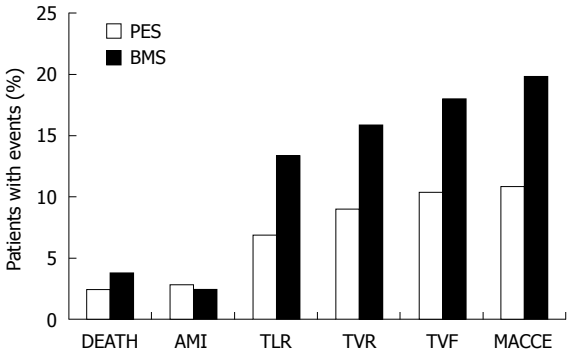


Figure 3 Results at 18 mo. EUCATAX trial. AMI: Acute myocardial infarction; MACCE: Major adverse cardiovascular events; TVF: Target vessel failure; TLR: Target lesion revascularisation; TVR: Target vessel revascularisation; PES: Paclitaxel-eluting stents; BMS: Bare-metal stent.

cardiac death, MI and stroke were similar, although PES showed a lower incidence of TLR and TVR driving a significant reduction in target vessel failure (TVF) and MACCE compared with the BMS design, and both were the major end points of the study. The incidence of any stent thrombosis was 1.4% in the PES group and 1.9% in the BMS group. Interestingly, beyond 1 year, no patient in the PES arm suffered stent thrombosis.

Baseline and follow-up angiographic findings are shown in Table 2. Follow-up angiography was performed in all 150 patients scheduled. In segment late luminal loss was 0.50 mm in the PES group and 0.94 mm in the BMS group ($P = 0.001$). The binary restenosis rate was 13.2% (13/98 lesions) in the PES arm and 34% (30/88 lesions) in the BMS arm ($P < 0.001$). Intravascular ultrasound showed no difference in late incomplete stent mal-apposition between groups (Table 2), although the incidence of late incomplete mal-apposition in the proximal segment of the stent was significantly in favor of the PES group ($P = 0.015$).

Table 2 Quantitative coronary analysis for both groups in the EUCATAX trial *n* (%)

	PES	BMS	*P* value
Baseline QCA analysis	*n* = 169	*n* = 153	
Reference diameter (mm)	2.75 ± 0.5	2.85 ± 0.5	0.086
Minimal luminal diameter (mm)	0.86 ± 0.4	0.85 ± 0.5	0.780
Lesion length (mm)	16.2 ± 6.1	15.6 ± 6.3	0.410
Stent diameter (mm)	21.7 ± 5.6	20.0 ± 4.8	0.160
Stent size (mm)	2.96 ± 0.4	2.93 ± 0.5	0.780
Immediately Post PCI QCA analysis			
Reference diameter (mm)	2.91 ± 0.44	2.96 ± 0.43	0.340
Minimal luminal diameter (mm)	2.68 ± 0.42	2.72 ± 0.43	0.400
Follow up QCA analysis	*n* = 98	*n* = 88	
Reference diameter (mm)	2.75 ± 0.48	2.75 ± 0.36	0.990
Minimal luminal diameter (mm)	2.16 ± 0.51	1.81 ± 0.75	0.007
Stenosis diameter (%)	27.4 ± 29.8	39.6 ± 23.9	0.005
Acute gain	1.82 ± 0.47	1.87 ± 0.62	0.450
Net gain	1.30 ± 0.49	0.93 ± 0.63	0.002
Late loss (in-stent)	0.52 ± 0.59	0.94 ± 0.70	0.002
Late loss (in-segment)	0.50 ± 0.56	0.91 ± 0.069	0.001
Angiographic restenosis	13 (13.2)	31 (35.2)	0.001
Follow up intravascular ultrasound analysis	*n* = 45	*n* = 37	
Stent length (mm)	21.7 ± 5.6	20.0 ± 4.8	0.160
Stent size (mm)	2.96 ± 0.4	2.93 ± 0.5	0.780
Incomplete stent apposition	5 (11.1)	9 (24.3)	0.150
Proximal segment	1 (2.2)	8 (21.6)	0.015
Body segment	2 (4.4)	1 (2.7)	1.000
Distal segment	2 (4.4)	0 (0.0)	0.500

QCA: Quantitative coronary analysis; PCI: Percutaneous coronary intervention; BMS: Bare-metal stent.

The study had a small sample size, a short-term outcome and a higher amount of late loss.

SUMMARY AND PERSPECTIVE

Since the introduction of the first DES designs, we have a strong clinical evidence for their significant benefits in terms of reduction of angiographic and clinical restenosis, which has been the Achilles heel of PCI during the past 30 years. However, although uncommon, we have also identified the potential deleterious effects of late and very late stent thrombosis associated with the implantation of these devices. Therefore, we clearly understand the complex process of designing the ideal DES, in which a combination of safety and efficacy should be the main goal.

Currently, we clearly recognize the advantages and disadvantages of the first DES designs in comparison with BMS, either in short- or long-term outcomes. However, little is known about the new DES generation in comparison with either BMS or the first DES designs. In the current review we report the short-term outcomes of new DES designs with BIO polymers either with respect to the first DES or to BMS designs. The results from these trials are presented in Table 3. Theoretically, BIO polymers have the advantage of complete degradation of

Table 3 Comparison between published trials of biodegradable eluting stents

Name	Stent design	Cardiac death	Cardiac death or MI	MI	TVR	TLR
LEADERS[28]	Biomatrix	2.1	6.7	5.8	7.8	6.5
	Cypher	2.7	6.6	4.6	9.9	7.4
	Nobori	0.0	-	4.7	7.1	0.0
NOBORI[34]	Taxus	0.0	-	8.6	14.3	2.9
ISAR-TEST-3[35]	Biodegradable polymer stent	2.0	2.5	1.5	-	5.9
	Permanent polymer sirolimus	2.0	3.5	2.0	-	7.9
	Polymer free sirolimus	2.0	4.0	2.5	-	12.9
ISAR-TEST-4[36]	Biodegradable polymer	2.8	6.3	4.3	13.7	8.8
	Control[1]	3.2	6.2	4.1	13.9	9.4
EUCATAX[39]	PES	1.9	4.7	2.8	8.2	6.1
	BMS	1.9	4.3	2.4	15.0	12.6

[1]Control reflects results of Cypher (Cordis, Florida, USA) or Xience (Abbott Vascular, Abbott Park, IL, USA). MI: Myocardial infarction; TVR: Target vessel revascularization; TLR: Target lesion revascularization; ISAR: Individualized Drug Eluting Stent System to Abrogate Restenosis.

the polymer together with the immunosuppressive agent that was loaded on it, after which only a BMS remains in place. Thus, all side effects related to durable polymers would be avoided or minimized with this type of coating. Requirements for dual antiplatelet therapy over a long period, mandatory with SES and PES with durable polymers, would now be necessary only within the period before polymer degradation. Long-term antiplatelet therapy is one of the major limitations for Cypher and Taxus implantation, especially in older patients or in patients with concomitant non-cardiac vascular or non-vascular illness requiring surgery. Consequently, there is plenty scope to improve the safety profile of the first DES generation; however, are these new stents with BIO polymers the answers to our concerns?

If we look at the results from the randomized LEADERS[28] and NOBORI[34] trials, with stent designs that share an identical polymer and drug, we do not see any advantage in terms of efficacy and safety in comparison with the old SES design. Even though the LEADERS study met the criteria for non-inferiority for the BioMatrix-Flex stent at 12 mo of follow-up, if we exclude the subgroup of patients with STEMI, we do not see any advantages in terms of safety in relation to the SES with a durable polymer (Cypher). Furthermore, the rate of non-STEMI reported in this trial with a BIO polymer stent (BioMatrix-Flex) design appears to be higher than we would expect. In addition, analysis from the subgroup of patients with STEMI had the bias of a high number of stent thromboses in the Cypher arm (over 8%), which was never reported in any randomized study in patients with STEMI with this DES design in the first year of follow-up[42].

The ISAR-TEST-4 trial[36] also reported a randomized head-to-head comparison between a BIO polymer SES *vs* 2 different durable coating DES designs, Cypher and Xience V. The ISAR BIO DES design had sirolimus completely released within the first 29 d, although the polymer disappeared between 6 and 9 wk after stent deployment. Therefore, the polymer in the stent remained in place around 1 mo after the release of the drug. For this reason, we cannot discard some adverse effects related to the polymer, free of drug, during that time. One- and two-year outcomes of this positive non-inferiority trial did not demonstrate any safety or efficacy advantage compared with the durable polymer arms, and the incidence of stent thrombosis was similar in all groups. Also, a late luminal catch up loss phenomenon between 8 mo and 2 years was reported in the ISAR-TEST-4 trial with the BIO polymer stent, a finding which was also commonly reported after implantation of SES (Cypher) with a durable polymer[37]. Taking into account that the drug and the polymer did not simultaneously disappear, an inflammatory response to coating breakdown cannot be discarded with this stent design.

In the PAINT trial[38], in both BIO stent designs the polymer remained in place for several months after the drug was completely eluted; therefore, an inflammatory response in response to the polymer itself and during the degradation process should be strongly considered.

In the EUCATAX trial[39], the BIO DES design allowed the polymer and the immunosuppressive drug to disappear simultaneously in the first 6 to 8 wk after deployment of the stent; beyond that time, a BMS with camouflage nanocoating remained in place. The camouflage nanocoating design has been linked with the safety outcome in promoting stent re-endothelialization and seems very useful in patients with a high-risk thrombotic profile such as STEMI or who underwent non-cardiac surgery soon after stent deployment. Interestingly, in a previous study with this kind of coating, intravascular ultrasound in patients with STEMI did not detect late acquired stent mal-apposition during follow-up angiography[43].

If we compare the EUCATAX with the LEADERS trial, which share similar clinical and angiographic inclusion criteria, excluding a significant lower late loss in favor of the LEADERS stent designs, the dual DES coating of EUCATAX showed similar rates of cardiac events including TLR, TVR and MI, although in the EUCATAX trial a trend of lower rates of MI and stent thrombosis were seen (Table 4). However, the down side of the last study was the large amount of late loss determined in the late angiography study with the EUCATAX stent design, which was higher than we expected (Table 2). Thus, we

Table 4 Comparison of baseline characteristics and follow up angiographic and clinical results from the randomized LEADERS[28] and EUCATAX[39] trials

Patients characteristics	BioMatrix	Cypher	EucaTax	*P* values
No. of patients	857	850	211	
Age (yr)	65 ± 11	65 ± 11	63.8 ± 10.2	0.32
Male gender	75.0	75.0	83.4	0.62
Hypertension	74.0	73.0	64.0	0.46
Diabetes mellitus	26.0	23.0	23.2	0.49
Hypercholesterolemia	65.0	68.0	56.9	0.36
Smoking	24.0	25.0	21.3	0.68
Previous MI	32.0	33.0	20.4	0.02
Previous PCI	36.0	37.0	35.5	0.93
Multi vessel disease	37.0	32.0	55.0	< 0.001
Clinical presentation				
Acute coronary syndrome	55.0	56.0	59.7	0.80
Lesions per patient				
> 1 lesion	29.0	22.0	26.1	0.09
Small vessels[1]	68.0	69.0	60.3	0.45
Procedural characteristics				
Stents per lesion	1.3 ± 0.7	1.3 ± 0.7	1.36 ± 0.5	0.38
Stent length per lesion (mm)	24.7 ± 15.5	24.6 ± 14.8	21.7 ± 5.6	0.006
Angiographic follow-up				
In-stent late loss	0.08 ± 0.4	0.15 ± 0.4	0.52 ± 0.6	< 0.001
Stent thrombosis[2]				
Overall stent thrombosis	3.6	3.3	1.4	0.28
Definite ST				
0-30 d	1.6	1.6	0.5	0.43
> 30 d-12 mo	0.4	0.5	0.9	0.52
0 d-12 mo	2.0	2.0	1.4	0.82
Efficacy endpoints at 12 mo				
Any TLR	6.5	7.4	6.1	0.63
Any TVR	7.8	9.9	8.2	0.23
Safety endpoints at 12 mo				
All causes of death	3.2	3.3	2.4	0.80
Cardiac death	2.1	2.7	1.9	0.66
Myocardial infarction	5.8	4.6	2.8	0.11
Cardiac death or MI	6.7	6.6	4.7	0.46

[1]Small vessel was defined as any vessel diameter with less than 2.75 mm; [2]Stent thrombosis definition by the Academic Research Consortium. MI: Myocardial infarction; PCI: Percutaneous coronary intervention; RVD: Reference vessel diameter; QCA: Quantitative coronary angiography; MLD: Minimal luminal diameter; DS: Diameter stenosis; TLR: Target lesion revascularization; TVR: Target vessel revascularization.

cannot exclude an inflammation process as a result of a crack in the PLGA coating, suggesting a possible breakdown of the polymer during the degradation process. We have to recognize that the degradation process of the BIO polymers is not always uniform; in poorly vascularized areas this process is likely to be slow, whereas in inflammatory areas it may be accelerated; consequently, if the drug elutes faster than the polymer, the advantage of the BIO polymer disappears.

CONCLUSION

Introduction of completely BIO instead of durable polymers has the potential to avoid or minimize some of the side effects related to the first DES designs. One year follow-up results from these randomized trials have demonstrated similar safety/efficacy profiles with this new DES technology using BIO polymers when compared with durable polymer designs (LEADERS and ISAR trials). However, these similarities do not mean any superiority in terms of reduction of stent thrombosis, the Damocles sword of the first DES technology. Equivalency in efficacy requires longer follow-up assessment.

Dual coating technology using an antithrombotic layer behind the PLGA coating is promising in terms of safety, although its value in terms of efficacy is questionable and needs further assessment. Consequently, the complex process of designing a DES with BIO polymers remains a challenge.

REFERENCES

1 **Sousa JE**, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, Kozuma K, Van Langenhove G, Sousa AG, Falotico R, Jaeger J, Popma JJ, Serruys PW. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001; **104**: 2007-2011

2 **Morice MC**, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnàr F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002; **346**: 1773-1780

3 **Moses JW**, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, Caputo RP, Kereiakes DJ, Williams DO, Teirstein PS, Jaeger JL, Kuntz RE. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003; **349**: 1315-1323

4 **Grube E**, Silber S, Hauptmann KE, Mueller R, Buellesfeld L, Gerckens U, Russell ME. 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* 2003; **107**: 38-42

5 **Colombo A**, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, Dudek D, Fort S, Schiele F, Zmudka K, Guagliumi G, Russell ME. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003; **108**: 788-794

6 **Stone GW**, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, Turco M, Caputo R, Bergin P, Greenberg J, Popma JJ, Russell ME. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004; **350**: 221-231

7 **Virmani R**, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tespili M, Valsecchi O, Kolodgie FD. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004; **109**: 701-705

8 **Togni M**, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, Meier B, Hess OM. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. *J Am Coll Cardiol* 2005; **46**: 231-236

9 **Hong MK**, Mintz GS, Lee CW, Park DW, Park KM, Lee BK, Kim YH, Song JM, Han KH, Kang DH, Cheong SS, Song JK, Kim JJ, Park SW, Park SJ. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation* 2006; **113**: 414-419

10 **Kotani J**, Awata M, Nanto S, Uematsu M, Oshima F, Minamiguchi H, Mintz GS, Nagata S. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol* 2006; **47**: 2108-2111

11 **Joner M**, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E,

Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 2006; **48**: 193-202
12 **Meier P**, Zbinden R, Togni M, Wenaweser P, Windecker S, Meier B, Seiler C. Coronary collateral function long after drug-eluting stent implantation. *J Am Coll Cardiol* 2007; **49**: 15-20
13 **Finn AV**, Joner M, Nakazawa G, Kolodgie F, Newell J, John MC, Gold HK, Virmani R. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation* 2007; **115**: 2435-2441
14 **Nakazawa G**, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. *Circulation* 2008; **118**: 1138-1145
15 **Cook S**, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, Vogel R, Hess O, Meier B, Windecker S. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007; **115**: 2426-2434
16 **McFadden EP**, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, Suddath WO, Weissman NJ, Torguson R, Kent KM, Pichard AD, Satler LF, Waksman R, Serruys PW. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; **364**: 1519-1521
17 **Iakovou I**, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, Airoldi F, Chieffo A, Montorfano M, Carlino M, Michev I, Corvaja N, Briguori C, Gerckens U, Grube E, Colombo A. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; **293**: 2126-2130
18 **Spertus JA**, Kettelkamp R, Vance C, Decker C, Jones PG, Rumsfeld JS, Messenger JC, Khanal S, Peterson ED, Bach RG, Krumholz HM, Cohen DJ. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006; **113**: 2803-2809
19 **Rodriguez AE**, Mieres J, Fernandez-Pereira C, Vigo CF, Rodriguez-Alemparte M, Berrocal D, Grinfeld L, Palacios I. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J Am Coll Cardiol* 2006; **47**: 205-207
20 **Rodriguez AE**, Rodriguez-Granillo GA, Palacios IF. Late stent thrombosis: the Damocle's sword of drug eluting stents? *EuroIntervention* 2007; **2**: 512-517
21 **Daemen J**, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Jüni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. 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* 2007; **369**: 667-678
22 **Byrne RA**, Iijima R, Mehilli J, Pinieck S, Bruskina O, Schömig A, Kastrati A. Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc Interv* 2009; **2**: 291-299
23 **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* 2009; **2**: 300-302
24 **Jiménez-Quevedo P**, Sabaté M, Angiolillo DJ, Costa MA, Alfonso F, Gómez-Hospital JA, Hernández-Antolín R, Bañuelos C, Goicolea J, Fernández-Avilés F, Bass T, Escaned J, Moreno R, Fernández C, Macaya C. 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* 2006; **47**: 2172-2179
25 **Grube E**, Dawkins K, Guagliumi G, Banning A, Zmudka K, Colombo A, Thuesen L, Hauptman K, Marco J, Wijns W, Joshi A, Mascioli S. TAXUS VI final 5-year results: a multicentre, randomised trial comparing polymer-based moderate-release paclitaxel-eluting stent with a bare metal stent for treatment of long, complex coronary artery lesions. *EuroIntervention* 2009; **4**: 572-577
26 **Kukreja N**, Onuma Y, Daemen J, Serruys PW. The future of drug-eluting stents. *Pharmacol Res* 2008; **57**: 171-180
27 **Finn AV**, Kolodgie FD, Harnek J, Guerrero LJ, Acampado E, Tefera K, Skorija K, Weber DK, Gold HK, Virmani R. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation* 2005; **112**: 270-278
28 **Windecker S**, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, Lenk K, Ischinger T, Klauss V, Eberli F, Corti R, Wijns W, Morice MC, di Mario C, Davies S, van Geuns RJ, Eerdmans P, van Es GA, Meier B, Jüni P. Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* 2008; **372**: 1163-1173
29 **Rodriguez AE**. Emerging drugs for coronary restenosis: the role of systemic oral agents the in stent era. *Expert Opin Emerg Drugs* 2009; **14**: 561-576
30 **Aoki J**, Ong AT, Abizaid A, den Heijer P, Bonnier H, McClean DR, Verheye S, Belardi J, Condado JA, Pieper M, Sousa JE, Bressers M, Symons J, Litvack F, Sianos G, Serruys PW. One-year clinical outcome of various doses and pharmacokinetic release formulations of paclitaxel eluted from an erodable polymer - Insight in the Paclitaxel In-Stent Controlled Elution Study (PISCES). *EuroIntervention* 2005; **1**: 165-172
31 **Onuma Y**, Serruys P, den Heijer P, Joesoef KS, Duckers H, Regar E, Kukreja N, Tanimoto S, Garcia-Garcia HM, van Beusekom H, van der Giessen W, Nishide T. MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in de novo coronary stenoses. *Eur Heart J* 2009; **30**: 1477-1485
32 **Han Y**, Jing Q, Xu B, Yang L, Liu H, Shang X, Jiang T, Li Z, Zhang H, Li H, Qiu J, Liu Y, Li Y, Chen X, Gao R. Safety and efficacy of biodegradable polymer-coated sirolimus-eluting stents in "real-world" practice: 18-month clinical and 9-month angiographic outcomes. *JACC Cardiovasc Interv* 2009; **2**: 303-309
33 **Ostojic M**, Sagic D, Beleslin B, Jung R, Perisic Z, Jagic N, Nedeljkovic M, Mangovski L, Milosavljevic B, Stojkovic S, Orlic D, Antonic Z, Miloradovic V, Topic D, Paunovic D. First clinical comparison of Nobori -Biolimus A9 eluting stents with Cypher- Sirolimus eluting stents: Nobori Core nine months angiographic and one year clinical outcomes. *EuroIntervention* 2008; **3**: 574-579
34 **Chevalier B**, Silber S, Park SJ, Garcia E, Schuler G, Suryapranata H, Koolen J, Hauptmann KE, Wijns W, Morice MC, Carrie D, van Es GA, Nagai H, Detiege D, Paunovic D, Serruys PW. Randomized comparison of the Nobori Biolimus A9-eluting coronary stent with the Taxus Liberté paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the NOBORI 1 trial--Phase 2. *Circ Cardiovasc Interv* 2009; **2**: 188-195
35 **Mehilli J**, Byrne RA, Wieczorek A, Iijima R, Schulz S, Bruskina O, Pache J, Wessely R, Schömig A, Kastrati A. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. *Eur Heart J* 2008; **29**: 1975-1982
36 **Byrne RA**, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz KL, Schulz S, Pache J, Fusaro M, Seyfarth M, Schömig A, Mehilli J. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial.

Eur Heart J 2009; **30**: 2441-2449
37 **Byrne RA**, Kastrati A. Biodegradable polymer limus-eluting stents are noninferior to permanent polymer-based stents: the ISAR-TEST-4 trial. *Interv Cardiol* 2010; **2**: 267-273
38 **Lemos PA**, Moulin B, Perin MA, Oliveira LA, Arruda JA, Lima VC, Lima AA, Caramori PR, Medeiros CR, Barbosa MR, Brito FS Jr, Ribeiro EE, Martinez EE. Randomized evaluation of two drug-eluting stents with identical metallic platform and biodegradable polymer but different agents (paclitaxel or sirolimus) compared against bare stents: 1-year results of the PAINT trial. *Catheter Cardiovasc Interv* 2009; **74**: 665-673
39 **Rodriguez AE**, Vigo CF, Delacasa A, Mieres J, Fernandez-Pereira C, Bernardi V, Bettinoti M, Rodriguez-Granillo AM, Rodriguez-Granillo G, Santaera O, Curotto V, Rubilar B, Tronge J, Palacios IF, Antoniucci D. Efficacy and safety of a double-coated paclitaxel-eluting coronary stent: The EUCATAX trial. *Catheter Cardiovasc Interv* 2011; **77**: 335-342
40 **Ozbek C**, Mailänder C, Schilling U, Bach R. Clinical efficacy of a DE stent after an electively planned percutaneous coronary intervention under "real-life" conditions: prospective registry (first-in-man data). *Clin Hemorheol Microcirc* 2008; **39**: 311-321
41 **Hoffmann M**, Horres R, Keller R, Baumann H. Isolation and characterisation of endothelial cell surface heparan sulphate from whole bovine lung for coating of biomaterials to improve haemocompatibility. In: Chiellini E, Sunamoto J, Migliaresi C, Ottenbrite RM, Cohn D, editors. Biomedical polymers and polymer therapeutics. New York, Boston, Dordrecht, London, Moscow: Kluwer Academic Publishers, 2002: 213-226
42 **Kastrati A**, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M, Di Lorenzo E, Kaiser C, Tierala I, Mehilli J, Seyfarth M, Varenne O, Dirksen MT, Percoco G, Varricchio A, Pittl U, Syvänne M, Suttorp MJ, Violini R, Schömig A. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007; **28**: 2706-2713
43 **Perez G**, Rodriguez-Granillo AM, Mieres J, Llaurado C, Rubilar B, Risau G, Fernandez-Pereira C, Rodriguez AE. 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* 2009; **21**: 378-382

S- Editor Cheng JX **L- Editor** Cant MR **E- Editor** Zheng XM