Advantages and disadvantages of biodegradable platforms in drug eluting stents

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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.

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

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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)\(^6\). During these years, we have also learned that some adverse effects, although rarely present, are more frequently associated with DES implantation\(^5\), some of them can be linked to durable polymers, which were continually present in the first DES designs\(^3\). Delayed healing, endothelial dysfunction, chronic arterial wall inflammation and late-acquired stent mal-apposition are more frequently linked with DES im-
release and elution of the immunosuppressive agent after uncovering, mal-apposition, endothelial dysfunction and the risk of late complications such as stent strut inflammatory response, with the potential for decreases in 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. 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; Taxustm, 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/cm², 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/mm² paclitaxel; 10% of the paclitaxel is released within 2 wk after stent deployment, although 90% of it remains in the polymer forever.

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, 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. BIO polymers allow the complete release and elution of the immunosuppressive agent after degradation of the polymer. Therefore, long-term antiplatelet therapy would not be required after the polymer completely disappeared. The most common BIO polymers are composed of poly(lactic 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. 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. 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) trial, NOBORI Individualized Drug Eluting Stent System to Abrogate Restenosis (ISAR)-TEST-3 and TEST-4 with sirolimus (rapamycin), PAINT (percutaneous intervention with BIO-polymer based paclitaxel-eluting or sirolimus-eluting vs bare stents for de novo coronary lesions) and EUCATAX trials. Study and stent design of each trial is described in Table 1.

LEADERS TRIAL

The LEADERS trial 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.
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-
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 glyocalyx against an equivalent BMS (Eucatech AG, Reinshelfeden; 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 module. The double coating includes a BIO polymer as the platform for paclitaxel elution and a glyocalyx to increase hemocompatibility. The glyocalyx 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,
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 was significantly in favor of the PES group ($P = 0.015$).

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
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\cite{38} and NOBORI\cite{28} 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\cite{38}.

The ISAR-TEST-4 trial\cite{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\cite{39}. 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\cite{42}, 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\cite{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\cite{42}.

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

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**Table 3** Comparison between published trials of biodegradable eluting stents

| Name          | Stent design          | Cardiac death | Cardiac death or MI | MI   | TVR | TLR |
|---------------|-----------------------|---------------|---------------------|------|-----|-----|
| LEADERS\cite{39} | 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\cite{38} | Taxus                 | 0.0           | -                   | 8.6  | 14.3| 2.9 |
| ISAR-TEST-3\cite{36} | 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\cite{36} | Biodegradable polymer | 2.8           | 6.3                 | 4.3  | 13.7| 8.8 |
|               | Control               | 3.2           | 6.2                 | 4.1  | 13.9| 9.4 |
| EUCATAX\cite{39} | PES                   | 1.9           | 4.7                 | 2.8  | 8.2 | 6.1 |
|               | BMS                   | 1.9           | 4.3                 | 2.4  | 15.0| 12.6|

1Control 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.
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.

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