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Research Article

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Drug-Eluting Balloon for Coronary In-Stent Restenosis: Could it be an Emerging Strategy?

Rasit Dinc*

Invamed Medical Innovation Institute, Ankara/Turkey

***Corresponding Author**
Rasit Dinc, Invamed Medical Innovation Institute, Turkey

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Abstract

Despite significant improvement in PCI, including drug-eluting stent (DES) applications, in-stent restenosis (ISR) remains a problem. ISR is challenging to manage. Repeat stenting with bare metal stent (BMS), repeat stenting with DES and bioresorbable vascular scaffolds is primarily used to prevent and treat ISR. Current European guidelines recommend DES or a drug-eluting balloon (DEB) to treat ISR with a Class I indication. However, its use in coronary artery interventions has not yet been approved in the United States. DEB allows the application of the antiproliferative drug to the ISR site without leaving an additional layer of stent strut. Studies show that DEB is superior to plain balloon alone and comparable to DES in ISR treatment. They are increasingly preferred due to their good therapeutic effect in preventing intimal proliferation and restenosis.

This review aims to provide an overview on the feasibility of using DEB in ISR management based on current knowledge.

Keywords: Coronary Artery Disease, In-Stent Restenosis (Isr), Drug-Coated Balloon, Drug-Eluting Balloon, Bare Metal Stent, Drug-Eluting Stent

1. Introduction

Coronary artery disease (CAD), which is the most common form of heart disease, remains one of the leading causes of mortality and morbidity worldwide [1]. Advances in percutaneous intervention (PCI) have led to dramatic advances in the treatment of coronary heart disease (2). Intracoronary stenting has become an important therapeutic option in the treatment of CAD, and PCI is performed on millions of people worldwide each year [2,3].

Balloon angioplasty (BA), the first PCI, was found to be effective in providing patency in the lumen diameter of the narrowed coronary artery [4]. However, early restenosis, caused primarily by vascular remodeling/elastic retraction, has compromised the results of BA [5]. Bare metal stents (BMS) were used as a rescue intervention scenario against these situations [6]. Although the introduction of BMS largely solved this early problem, restenosis in the stent (ISR) negatively affected long-term results [7,8]. Current treatment for coronary ISR usually involves angioplasty followed by placement of an additional drug-eluting stent (DES). This has been shown to be superior to BA alone in reducing subsequent restenosis [9]. Although a more drastic improvement has been observed with drug-eluting stent (DES) applications, ISR remains a challenge [2,3]. Even with the new generation of DESs and bioresorbable vascular scaffolds currently being developed, this problem could not be completely prevented in the long term [6]. Approximately 5% to 10% of patients who undergo coronary intervention with DES experience ISR in the first year [10]. About 10% of PCI is performed for the treatment of ISR. DES- associated ISR treatment potentially has increased complexity and worse clinical outcomes than revascularization of de novo lesions [11]. The best management strategy for ISR continues to be a matter of debate. In the United States, it is most commonly treated with repeated placement of a drug-eluting stent, that is, placement of the stent in the stent [10].

In recent years, drug-eluting balloons (DEB) have become a new treatment strategy for CAD [2]. The strategy is based on the combination therapy of balloon and drug without leaving a permanent implant [12]. DEB is designed for the application of antiproliferative agents to coronary lesions, especially in restenosis of the stent. Based on the rationale for the highly lipophilic property of the drug in an excipient, even short contact times between the balloon surface and the vessel wall are sufficient for its effective distribution (9). In this way, lower restenosis rates are achieved [2,12].

This review aims to provide the reader with an overview of the feasibility of the use of DEB catheters in the management of ISR in light of current information.

2. Pathophysiology of In-Stent Restenosis

Knowing and evaluating the underlying etiology of ISR is crucial to guide and optimize interventions to prevent recurrent ISR. Different mechanisms play a role in the development, severity, and patterns of ISR, including factors related to the patient (age, diabetes mellitus, genetics, etc.), factors related to the lesion (type, length, location of the lesion, arterial size, etc.), procedural factors (type, length, expansion size, number of stents, etc.) [13,14]. These traditional mechanisms in BMS-associated ISR may also apply to DES-associated ISR [11]. The main problem in the use of metallic stents is the formation of thrombuses and vascular inflammation resulting from permanent placement of foreign material within the coronary artery. Both cause neointimal hyperplasia due to arterial damage and ultimately lead to gradual narrowing of the stented coronary artery lesion, defined as ISR [15]. Although complex and not yet fully understood, the mechanisms underlying stenosis are believed to involve the following basic steps: endothelial cell denudation due to stenting, initiation of inflammatory migration, and vascular smooth muscle cells (VSMC), resulting in neointimal hyperplasia and neo-atherosclerosis [16]. Increased mitogens and cytokines in the circulation as a result of endothelial denudation cause increased proliferation and migration of VSMC and inflammatory cells [17]. In addition, VSMCs change from a quiescent contractile phenotype to a synthetic phenotype [18].

On the one hand, DESs minimize the proliferation of neointima. On the other hand, polymer and drug hypersensitivity, local inflammation, and delayed healing contribute to the formation of DES-associated neointima [11]. The main disparities between ISR in BMS and DES are in time of presentation, morphological patterns, underlying substrate, and response to the type of stent used in the intervention [19]. BMS-associated ISR tends to present as homogeneous hyperplasia, while DES-associated ISR tends to be focal due to the localized inflammatory response, especially at the edge of the stent or at the fracture sites of the stent [2,19]. Furthermore, compared to BMS-ISR, focal neo-atherosclerosis occurs both more frequently and significantly earlier in DES-ISR (approximately 900 days vs 70 days) [20].

3. Drug Eluting Balloons in the Treatment of in-Stent Restenosis

Management of ISR is challenging due to its heterogeneous mechanisms and relatively high relapse rate and clinical presentation of patients. The type and timing of the intervention must be carefully planned [14]. Intravascular ultrasound (IVUS) or optical coherence tomography (OCT) intravascular imaging plays an important role in elucidating the potential mechanism of ISR and is recommended to be used routinely [11,14]. Current European guidelines recommend that DES or DEB treat ISR with a Class I indication [9]. However, DEBs are not yet approved for use in coronary artery interventions in the United States by the Food and Drug Administration (FDA) [15].

There are other methods for preventing and treating ISR, including pharmacological (such as lipid-lowering or antiplatelet therapy) and device-based (such as angioplasty, cutting or scoring balloon therapy, debulking techniques, brachytherapy, repeat stenting with BMS, repeat stenting with DES, and bioresorbable vascular scaffolds) [11,14,21].

In de novo lesions, DES has become an attractive option in the treatment of neointimal hyperplasia in ISR associated with BMS because it substantially inhibits neointimal proliferation [11]. Sirolimus or paclitaxel-DESs were found to be significantly superior in preventing recurrent restenosis compared to BA and BMS alone [22,23]. Furthermore, treatment in patients who develop ISR associated with DES is both more difficult and has worse outcomes compared to patients with ISR associated with BMS [11,23,24].

Although its value in de novo lesions remains controversial, in recent decades the use of DEB has been shown to be very effective not only in patients with BMS-associated ISR but also in patients with DES-associated ISR [3,25-27].

DEBs consist of a semi-flexible monolayer balloon coated with antiproliferative agents encapsulated in a lipophilic matrix. These antiproliferative components, which can prevent the proliferation and migration of smooth muscle cells, rapidly infiltrate the wall of the blood vessel after balloon dilation and have a longer retention time due to their lipophilic nature, without leaving any layer of the stent strut behind (Figure 1) [14,22]. Paclitaxel is used mostly as an antiproliferative drug. It is more lipophilic and has faster cellular uptake compared to limus-based drugs. However, based on available clinical studies, there is no evidence of a 'class effect' of different DEB [9,28].

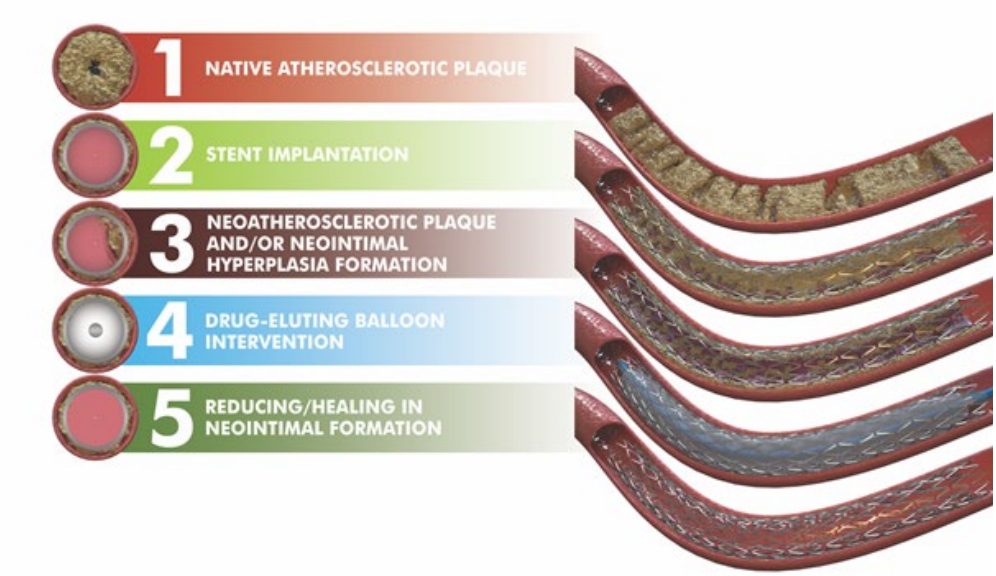

Figure 1. Schematic representation of the implantation and outcome of the drug-eluting balloon in instent restenosis.

4. Evidence for the indication of the use of DEB in ISR

Despite advances in DES technology, treatment of ISR remains a challenging clinical problem. Furthermore, the implantation of more than 2 metal stents in recurrent ISR lesions is likely to have a detrimental effect on long-term outcomes [11]. DEB, on the other hand, allows the administration of antiproliferative drug to the ISR area without leaving an additional layer of stent strut [12]. Studies show that DEB is superior to POBA alone and comparable to DES, including second-generation DES, in the treatment of BMS-associated ISR [26,29,30]. Furthermore, the superiority of DEB over POBA alone has been demonstrated not only in the treatment of BMS-associated ISR but also in the treatment of DES-associated ISR [31].

There are dozens of commercial DEB products around the world with different compositions and coating techniques, and therefore different pharmacokinetics [28]. Its basic components are the active ingredient, excipient, and balloon. Although different techniques are used in their production, the main objective is to meet clinical requirements such as continuous drug administration at therapeutic doses, maintaining drug concentration in the walls of blood vessels for a long time and not being toxic to the body [32]. Some of these selected are presented in Table 1. Furthermore, in general opinion, the general design of the Extender PTCA (Invamed, Ankara, Turkey) has been figured (Figure 2).

Device	Manufacturer	Antiproliferative drug	Excipient
Extender PTCA	Invamed (Ankara, Turkey)	Paclitaxel	Iopromid
IN.PACT Falcon	Medtronic (Dublin, Ireland)	Paclitaxel	Urea
Essential	iVascular (Sant Vicenç dels Horts, Spain)	Paclitaxel	Organic ester
Paccocath	Bayer (Leverkusen, Germany)	Paclitaxel	Iopromid
Agent	Boston Scientific (Massachusetts, USA)	Paclitaxel	Citrate ester
Pantera Lux	Biotronik (Bülach, Switzerland)	Paclitaxel	Butyryl-tri-hexyl citrate
Magictouch	Concept Medical Research (Gujarat, India)	Sirolimus	Phospholipid
Virtue	Caliber Therapeutics (Pennsylvania, USA)	Sirolimus	Porous balloon
Selution	M.A. Med Alliance (Mont-sur-Rolle, Switzerland)	Sirolimus	Cell attachment

Table 1: Some selected drug-eluting balloons in use around the world.

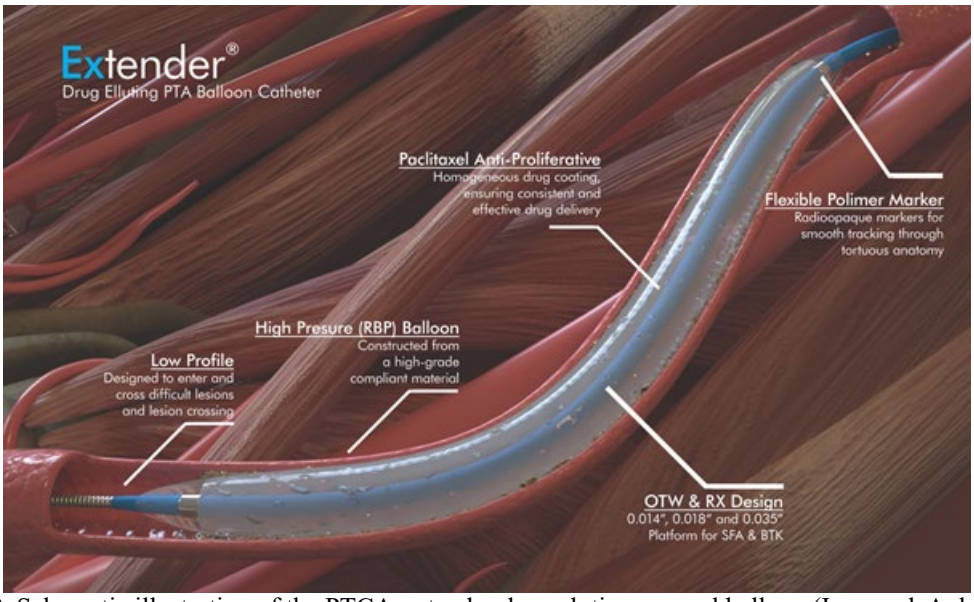

Figure 2. Schematic illustration of the PTCA-extender drug-eluting coronal balloon (Invamed, Ankara, Turkey).

In recent years, many clinical studies have been conducted that compare DEB with conventional treatments and establish its definitive effectiveness in the treatment of ISR (Table 2). While some of these products used paclitaxel as an antiproliferative drug, others used sirolimus and its derivatives. Studies show that these drugs have similar safety and effectiveness [2].

Control arm	Treatment History	Angiographic follow-up	Clinical follow-up	Clinical follow-up		Study/Ref.
		Outcomes*	FU time and p value	Outcomes*	FU time and p value	
PB	BMS	LLL: 0,03±0,48 mm vs. 0,74±0,86 mm	6-mo, p=0.002	MACE: 4% vs. 31%	12-mo, p=0.01	Scheller et al. (29)
DES-P	DES	LLL: 0,46±0,51 mm vs. 0,55±0,61 mm	9-mo, p<0.001	TLF: 17% vs. 16%,	12-mo, p=0.52	PEPCAD China ISR (33)
DES	DES	MLD: 1.80±0.60 mm vs. 2.03±0.70 mm	6-9-mo, p<0.001	MACE: 18% vs. 10%	12-mo, p=0.04	RIBS IV (30)
DES-E	BMS	MLD: 2.01±0.60 mm vs. 2.36±0.60 mm	9-mo, p<0.001	MACE: 8% vs. 6%	12-mo, p=0.60	RIBS V (26)
PB	DES	LLL: 0.18±0.45 mm vs. 0.72±0.55 mm	6-mo, p<0.001	MACE: 4% vs. 40%	12-mo, p=0.005	Habara et al (31)
DES-E	DES	MLD: 1.71±0.51 mm vs. 1.74±0.61 mm	6-mo, p=0.65	MACE: 10.9% vs. 9.2%	12-mo, p=0.66	Dare (34)
DES-E	DES	LLL: 0.03±0.40 mm vs. 0.21±0.70 mm	6-mo, p<0.001	TLF: 16.7% vs. 14.2%	12-mo, p<0.001	Biolux (35)
PB	Mixed	MLD: 2.10±0.45 mm vs. 2.13±0.49 mm	12-mo, p=0.24	TLF: 17.9% vs. 28.6%	12-mo, p=0.003	AGENT IDE (3)

*The first result is the DEB data, and the second is the data of the treatment that is being compared. Abbreviations: DEB, drug-eluting balloon; PB, plain; DES-P, paclitaxel-coated drug-eluting stent; DES-P, everolimus-coated drug-eluting stent; BMS, bare metal stent; MACE, major adverse cardiac events; LLL, late luminal loss; MLD, minimal lumen diameter; TLF, target lesion failure; TLR, target lesion revascularization; FU, follow-up.

Table 2: Examples of several selected randomized clinical trials comparing DEB with other treatments in the treatment of in-stent restenosis.

5. Discussion and Conclusions

Coronary ISR, which can cause recurrent ischemia and major adverse cardiac events, is difficult to manage due to its heterogeneous mechanisms and relatively high relapse rate [14]. Deliverability, efficiency, and security are the key features expected from an ideal PCI [17]. In this context, DEBs are an important alternative that has become a new treatment strategy for coronary artery disease in recent years. With DEB, which combine balloon angioplasty with drug delivery technology, lipophilic antiproliferative drugs are administered directly to the

target vessel to prevent excessive neointimal hyperplasia and restenosis, leaving no metal stent or polymer behind. This avoids potential complications and risks associated with stents [32,36]. Although many country guidelines, such as China and European countries, recommend DES or DEB for the treatment of ISR with Class I indication, DEBs are not approved for commercial use in coronary artery interventions in the United States [1]. In cases of in-stent restenosis where placing an additional layer of metal could be problematic (such as bifurcation lesions and patients who already have two or more layers of the stent), DEBs are particularly attractive [15].

Numerous studies have demonstrated the effectiveness and safety of DEBs in addressing ISR [37,38]. Data from these studies reveal that DBCs in the treatment of ISR offer some potential advantages, such as targeted drug delivery, decreased risk of thrombosis, and better long-term results.

Yeh et al. conducted a study based on the primary end point of the failure of the target lesion, defined as the combination of cardiac death, myocardial infarction related to the target vessel, and revascularization of the target lesion induced by ischemia [3]. Compared to PB, DEB treatment showed a lower rate of target lesion failure at 1-year follow-up in this study.

In their large meta-analysis including 27 studies with a total of 5,923 patients at 6 months to 1 year of follow-up, Siontis et al. found that repeat stent placement with DES was statistically superior to all other treatment modalities (BA alone, debulking techniques, brachytherapy, BMS) for both primary endpoints (including percent diameter stenosis) and secondary endpoints (including binary restenosis, TLR rates, myocardial infarction or death) [39]. In large meta-analyses by Giacoppo et al., which included 24 trials with a total of 4,880 patients, both DEB and DES were superior to other treatment modalities according to predefined clinical outcomes [37]. Ma et al. and Giacoppo et al. reported similarly in their meta-analyses that late luminal loss (LLL) appeared to be slightly lower in the DEB arm compared to DES [1,37]. However, it has been observed that there is a high level of heterogeneity among trials. Ma et al. also reported that DEB was not associated with a difference in the incidence of cardiovascular death and myocardial infarction compared to stents [1]. In the meta-analysis study by Scheller et al., paclitaxel-coated DEB was reported to be safer in terms of all-cause mortality, incidence of MI, and stent thrombosis of the target lesion during the 3-year follow-up period [29].

Together, data from RCTs indicate that DEBs are the second most effective treatment of ISR after PCI with DES. Repeated DES implantation, the most effective treatment for ISR, should be preferred to improve the long-term patency of restenotic lesions with more aggressive angiographic patterns (eg, diffuse or occlusive). DEBs may preferentially be used in less complex restenotic lesions (eg focal or edge-associated), to avoid the implantation of an additional stent layer, and in patients at high risk of bleeding who cannot tolerate long-term dual antiplatelet therapy [14].

Some studies have compared DEB and DES in the treatment of stent edge restenosis. Studies showed similar results in terms of efficacy and safety between DEB and DES [34,36,40].

DEB is increasingly preferred due to its good therapeutic effect in preventing intimal proliferation and restenosis. Although repeated DES implantation has generally been reported to be the best method among others in the treatment of ISR, there is a high level of heterogeneity between studies. Even in some subgroups, DEB, which is superior to uncoated techniques and, overall, the second most effective and safe method after DES, was found to be superior to DES. Although long-term follow-up has shown that DEB therapy is moderately less effective than repeated DES implantation, the 'leave nothing behind' strategy stands out as potentially safer compared to DES due to the lower risk of bleeding due to shorter DAPT and very late events related to the stent. To better assess the effectiveness and safety of DEB, larger clinical trials with long-term follow-up and a detailed evaluation may clarify the best treatment approach for coronary ISR.

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