Review Article

Applications of the Drug-Eluting Balloon in Coronary Artery Disease

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ABSTRACT

Percutaneous revascularization strategies have evolved significantly in the past decades. However, every new technology has advantages over the previous ones, but also carries new risks. Neointimal hyperplasia, associated with bare metal stents, and delayed strut endothelialization and vascular inflammatory reaction to the polymer, associated with drug-eluting stents, are examples of this premise. Drug-eluting balloons were developed with the aim to modulate neointimal hyperplasia after intervention, avoiding the late risks associated with drug-eluting stents. However, the evidence and recommendations for their use have not been adequately defined. This review aims to present and characterize the different types of drug-eluting balloons commercially available worldwide, reviewing the most relevant studies in the literature in different clinical scenarios and describe the main indications and recommendations for their use.

DESCRIPTORS: Coronary restenosis. Angioplasty, balloon, coronary. Percutaneous coronary intervention. Paclitaxel. Review.

RESUMO

Aplicações do Balão Farmacológico na Doença Arterial Coronária

As estratégias de revascularização percutânea evoluíram significativamente nas últimas décadas. No entanto, toda nova tecnologia apresenta um benefício sobre a anterior, mas traz consigo também novos riscos. A hiperplasia neointimal, associada aos stents não farmacológicos, e a endotelização tardia das hastes e reação inflamatória vascular ao polímero, associada aos stents farmacológicos, são exemplos dessa premissa. Os balões farmacológicos foram desenvolvidos com o racional de modular a hiperplasia neointimal após a intervenção e de não suscitar os problemas tardios relacionados aos stents com eluição de fármacos antiproliferativos. No entanto, as evidências e as recomendações para sua utilização ainda não foram adequadamente definidas. Esta revisão objetiva apresentar e caracterizar os tipos de balão farmacológico disponíveis no mercado mundial, fazendo uma revisão dos estudos mais relevantes presentes na literatura sobre seu uso nos diversos cenários clínicos e descrever as principais indicações e atuais recomendações para seu uso.

DESCRITORES: Reestenose coronária. Angioplastia coronária com balão. Intervenção coronária percutânea. Paclitaxel. Revisão.

Coronary balloon angioplasty was first performed by Andreas Gruentzig in 1977.[1] Although revolutionary, the procedure was not without risk. The balloons used could cause vessel dissection and acute occlusion, with the eventual need for emergency coronary artery bypass grafting (CABG), and were associated with the phenomena of elastic recoil and negative remodeling, chiefly responsible for the high rates of coronary restenosis, occurring in 30-40% of cases.[2]

At the end of the 1980s, conventional stents (bare metal stents) emerged as an alternative to balloon use. These devices were able to seal vessel dissections, avoiding the catastrophic acute complications of balloon angioplasty and countering the major mechanical phenomena hitherto related to restenosis.[3] However, the healing response to barotraumas sometimes led to an exaggerated neointimal hyperplasia, a substrate of intra-stent restenosis, with an incidence of 20-30% of cases.[4]

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Over the past 15 years, the advent of drug-eluting stents (DESs), with elution of drugs inhibiting neointimal hyperplasia, combined the benefits of the mechanical support offered by conventional platforms with their anti-proliferative effects, reducing restenosis rates to < 10%.[5] However, the rates of late and very late stent thrombosis observed with the use of DESs of the first generations – due to a delayed endothelialization of stent struts and the local inflammatory reaction induced by polymers – were causes of concern. Moreover, the need for prolonged dual antiplatelet therapy entailed a potential increased risk of bleeding, as well as difficulties in carrying out non-cardiac surgeries.[6]

In recent years, researchers have looked for alternatives that allow for the release of anti-proliferative drugs to the vascular endothelium without a long-term permanence of structures potentially associated with undesirable effects.[7] Some of these devices are: DES with bioabsorbable polymers; DES with no polymers; absorbable intravascular supports; and drug-eluting balloons (DEBs). Some of them are already approved for clinical use, while others are still under investigation, and have only been released for use in specific situations.

This literature review aimed to provide a more detailed discussion on DEBs, especially in relation to their composition, currently available platforms, indications and possible problems, as well as the results of major clinical studies that have used these devices in different situations.

RATIONALE FOR DRUG-ELUTING BALLOONS

From the pathophysiological point of view, DEBs attempt to preserve the benefits of a DES, trying to minimize some of its potential problems.[7] The main advantages of DEBs are: (1) quick and homogeneous release of the anti-proliferative drug to the vessel wall, which is absorbed and has a prolonged effect, attenuating the process of neointimal hyperplasia (by maintaining DES effectiveness); (2) absence of polymer, which can reduce or eliminate the vascular inflammatory response, which is directly linked to very late thrombosis events; (3) absence of the metal platform; (4) a lower device profile and greater navigability, reaching lesions in smaller caliber, tortuous, and calcified vessels; and (5) the need for a dual antiplatelet therapy for a shorter time.[7]

On the other hand, the absence of a metallic mesh can result in potential disadvantages. DEBs are not able to contain dissections as efficiently, and the implantation of a rescue BMS for treatment of complications is a strategy that still needs to be more deeply investigated. Moreover, the phenomenon of acute elastic recoil is not avoided, and there are doubts whether the application of these devices is able to control late negative remodeling.

TYPES OF DRUG-ELUTING BALLOON

Available evidence reveals that paclitaxel is the most effective drug used with DEB technology. This is due to its significant lipophilia, which allows for a more homogeneous distribution through the vessel wall, as well as a quick absorption and the duration of the effect, which may be extended for several days. With regards to drug release, there are several types of technology proposed for the transference of the agent to the vessel wall.[8]

The first DEBs available were the Paccocath™ (Bayer AG, Leverkusen, Germany) and SeQuent Please™ (B. Braun Melsungen, Berlin, Germany) balloons. On these platforms, paclitaxel (3 mg/mm^2) is mixed with the drug carrier, an iodinated hydrophilic contrast, iopromide, which is applied to the surface of the balloon. The contrast increases drug solubility, facilitating its transfer to the vessel wall. A pre-dilation of the lesion is accomplished with a conventional balloon measuring 0.5 mm less than the chosen DEB. The recommended time for DEB inflationis 60 seconds.[8]

A second type of DEB was the In.Pact Falcon™ (Invatec, Roncadelle, Italy). With this device, paclitaxel (3 mg/mm^2) is released by a hydrophilic spacer molecule, urea, which covers the balloon. The total drug elution time to the vessel wall was reduced to 30-60 seconds.

The third type was the DIOR™ (Eurocor, Bonn, Germany) balloon. With this device, the drug is combined with a hydrophilic resin that, when in contact with the tissue, opens its structure, allowing for a quick release of paclitaxel, induced by the inflated balloon. The balloon is provided folded, preventing the loss of anti-proliferative agent during navigation. The entire volume of paclitaxel (3 mg/mm^2) is released in a single 60 second inflation[8] (Table 1).

PRECLINICAL DATA

Pharmacokinetics

Preclinical studies showed that when cells are exposed to paclitaxel, the drug is retained for up to 6 days; and that a single dose is sufficient to maintain the anti-proliferative effects for up to 14 days.[9,10] In a porcine model, a prolonged DEB inflation resulted in a release of about 90% of the drug to the vessel wall and, after one hour, about 10 to 15% of the agent was still in place, indicating its quick transfer to endothelium, and a prolonged retention.[11]

Pharmacodynamics

DEB studies in animal models showed reduction of neointimal hyperplasia area on the order of 60%,[11-13] with significant reduction of stenosis diameter and late

TABLE 1
Major types of drug-eluting balloon and their characteristics.

Type of balloon	Manufacturer (country)	Principle	Characteristics
Paccocath™	Bayer AG (Germany)	Paclitaxel mixed with hydrophilic contrast, applied to the surface of the balloon.	80% of the anti-proliferative agent is transferred to the treated vessel segment (10-15% in the first inflation).
SeQuent Please™	B. Braun (Germany)		
In.Pact Falcon™	Invatec (Italy)	Paclitaxel is released from a natural hydrophilic excipient covering the balloon.	A faster total eluting time (a 30-60-second inflation).
DIOR™	Eurocor (Germany)	Paclitaxel is combined with a hydrophilic matrix, which, in contact with the tissue, opens its structure and allows quick drug release, induced by balloon inflation.	Drug release in a single prolonged inflation (60 seconds) or fractional release in quick inflations

lumen loss. It was also demonstrated that a single, quick inflation produces the same effects as several prolonged inflations.[14] An initial study on an experimental model showed that the Paccocath™ balloon was superior to the DIOR™ balloon, in relation to neointimal proliferation inhibition.[15]

MAJOR CLINICAL STUDIES WITH DRUG-ELUTING BALLOONS

Intra-stent restenosis

Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis (PACCOCATH ISR I), a randomized, double-blind, multicenter study, included patients with stable or unstable angina, and with a single restenotic lesion. 52 patients were randomized in a 1:1 ratio for treatment with angioplasty with a DEB (Paccocath™) or with a conventional balloon. The endpoints analyzed were: late lumen loss in the treated segment after 6 months (primary endpoint) and binary restenosis at 6 months, and major adverse cardiovascular events (MACE) at 12 months (secondary endpoints). Late lumen loss was significantly lower in the DEB (0.03 ± 0.48 mm vs. 0.74 ± 0.86 mm; $p = 0.002$) group. This group also showed lower binary restenosis (5% vs. 43%; $p = 0.002$) and MACE (4% vs. 31%; $p = 0.02$) rates.[16]

The PACCOCATH ISR I study was extended through the addition of a randomized group (ISR II); all patients were followed for 2 years. 108 patients were included, and the results of the pooled analysis confirmed the findings of individual studies. There was less late lumen loss (0.11 ± 0.45 vs. 0.81 ± 0.79 mm; $p <0.001$), a lower binary restenosis rate (6% vs. 51%; $p <0.001$) at 6 months, and a lower target-lesion revascularization rate at 12 months (4% vs. 37%, $p = 0.001$) and of MACE at 24 months (11% vs. 46%; $p = 0.001$) in the DEB group.[17]

Data from five years of clinical follow-up of patients randomized in the PACCOCATH ISR I and II studies were published. During this period, there was a significantly lower cumulative incidence of MACE in the group treated with DEB (27.8% vs. 59.3%; $p = 0.009$), mainly due to a reduced target lesion revascularization rate (9.3% vs. 38.9%, $p = 0.004$).[18]

Paclitaxel-Coated Balloon Catheter Versus Paclitaxel-Coated Stent for the Treatment of Coronary In-stent Restenosis (PEPCAD ISR II), a prospective, randomized, multicenter study, evaluated the safety and efficacy of the SeQuent Please™ drug-eluting balloon vs. the Taxus™ stent in patients with BMS restenosis. 131 individuals were included, and the analyzed outcomes were: Late lumen loss at 6 months (primary endpoint), and rate of binary restenosis and MACE after 6 months, 1 year, and 3 years (secondary endpoints). The late luminal loss was significantly lower with the SeQuent Please™ device (0.17 ± 0.42 mm vs. 0.38 mm $\pm$ 0.61; $p = 0.032$), as well as the rate of binary restenosis (7% vs. 20.3%, $p = 0.06$). At 36 months, MACE rate was numerically higher in the group of patients treated with Taxus™ (9.1% vs. 18.5%; $p = 0.14$), due to an increased rate of target-lesion revascularization (6.2 % vs. 15.4%, $p = 0.10$).[19]

Habara et al.[20] conducted, in Japan, a prospective, randomized, multicenter study that included 50 patients with restenosis of sirolimus-eluting stent, with the aim of evaluating the efficacy of treatment with DEB (SeQuent Please™) vs. conventional balloon. The primary endpoint was late lumen loss, assessed on an angiographic follow-up at 6 months, and the secondary endpoints were binary restenosis and MACE rates at 6 months. At the angiographic follow-up, obtained in 94% of patients, late lumen loss was lower in the DEB group (0.18 ± 0.45 mm vs. 0.72 ± 0.55 mm; $p = 0.001$). The rates of recurrent restenosis (8.7% vs. 62.5%; $p = 0.0001$) and target lesion revascularization (4.3% vs. 41.7%, $p = 0.003$) were also lower in the DEB group, which exhibited higher MACE-free survival (96% vs. 60%; $p = 0.005$).[20]

With similar characteristics to those of the previous study, but with a larger sample size, Treatment of

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DES-In-Stent Restenosis WithSeQuent™ Please Paclitaxel Eluting PTCA Catheter (PEPCAD-DES), a prospective multicenter randomized study conducted in Germany, included 110 patients with indication for treatment of DES (Cypher, Yukon™, Xience™, or Taxus™) restenosis, with the aim to compare the results of angioplasty with DEB (SeQuent Please™) and with conventional balloon angioplasty. The primary outcome assessed was late lumen loss at 6 months, and the secondary outcome was a combination of cardiac death, acute myocardial infarction (AMI) attributed to the target vessel, or target lesion revascularization. No differences were observed in baseline or procedure characteristics of patients, and the angiographic result was obtained in 91% of cases, with results similar to the previous study: DEB was superior to conventional balloon, with late lumen loss of 0.43 ± 0.61 mm vs. 1.03 ± 0.77 mm (p <0.001) and lower restenosis (17.2% vs. 58.1%, p <0.001), and its superiority was also observed in the combined clinical endpoint (16.7% vs. 50%, p <0.001).[21]

ISAR-DESIRE 3, a randomized open-label multicenter study conducted in Germany, compared the treatment of intra-stent restenosis with "limus-" family drug-elution stents with DEB (SeQuent Please™), paclitaxel-eluting stent, or conventional balloon (1:1:1). 402 patients were included in this study, and the primary outcome analyzed was the diameter of the stenosis on an angiographic follow-up at 6-8 months, obtained in 84% of patients. It was observed that DEB was not inferior compared to DES with respect to the diameter of the stenosis ($38.0 \pm 21.5\%$ vs. $37.4 \pm 21.8\%$, $p = 0.007$ for non-inferiority). These two strategies were superior compared to the conventional balloon ($54.1 \pm 25.0\%$, p for superiority < 0.0001 for both comparisons). The incidences of death, AMI, and stent thrombosis were similar between groups.[22]

Restenosis Intra-stent of Bare Metal Stents: Paclitaxel-eluting Balloon vs. Everolimus-eluting Stent (RIBS V), a randomized open-label multicenter prospective study, included 189 patients in Spain, with the aim to comparing the results of DEB (SeQuent Please™) versus everolimus-eluting stent (Xience PRIME™) for the treatment of intra-stent restenosis of BMS. The primary endpoint was the minimal luminal diameter on revaluation at nine months, performed in 92% of patients. In the DES group, the success rate was of 100% for stenting, but in the DEB group, 8% of patients required stenting after a suboptimal result of this strategy. In the DES group, a greater minimum lumen diameter (2.36 ± 0.6 mm vs. 2.01 ± 0.6 mm; $p < 0.001$), as well as a lower stenosis diameter rate ($13 \pm 17\%$ vs. $25 \pm 20\%$; $p < 0.001$) and greater net luminal gain (1.41 ± 0.6 mm vs. 0.99 ± 0.6 mm; $p < 0.001$) were observed. However, late lumen loss (0.04 vs. 0.5 mm vs. 0.14 ± 0.5 mm; $p = 0.14$) and binary restenosis (4.7% vs. 9.5%, $p = 0.22$) were low, and were similar between groups. The combined clinical

events (cardiac death, AMI, and target vessel revascularization; 6% vs. 8%; $p = 0.60$) and the need for target vessel revascularization (2% vs. 6%; $p = 0.17$) were similar in both groups. Despite the advantage of DES in angiographic outcomes, both DES and DEB provided satisfactory clinical results, with a low rate of clinical and angiographic recurrences.[23]

A meta-analysis of 801 patients pooled five studies evaluating DEB in the treatment of intra-stent restenosis: two of these studies compared DEB with Taxus™ stent (an arm of the ISAR DESIRE 3 study, and PEPCAD 2 ISR) and the other three compared DEB with balloon angioplasty (Habara et al.,[20] PACCOCATH, and PEPCAD DES). The endpoints chosen were MACE, mortality, AMI, target lesion revascularization, restenosis at the treated segment, and stent thrombosis. DEB was superior to its comparison (conventional balloon or Taxus™) with respect to MACE (relative risk – RR = 0.46; 95% CI: 0.31-0.70; $p < 0.001$), mainly due to the reduction of target lesion revascularization (RR = 0.34; 95% CI: 0.16-0.73; $p = 0.006$). The use of DEB was also associated with lower rates of restenosis in the segment (RR = 0.28; 95% CI: 0.14-0.58; $p < 0.001$) and lower late lumen loss (mean difference, -0.38 mm; 95% CI: -0.60 to -0.15 mm; $p = 0.001$). Reduced mortality (RR = 0.48; 95% CI: 0.24-0.95; $p = 0.034$) and no significant AMI reduction (RR = 0.68; 95% CI: 0.32-1.48; $p = 0.337$) were observed. The occurrence of stent thrombosis was very rare (one in each arm), and no difference was observed between groups (RR = 1.12; 95% CI: 0.23-5.50; $p = 0.891$). A subgroup analysis showed that the benefit of the use of DEB was higher, compared to control, in patients with BMS restenosis, whereas the effect was smaller in patients with DES restenosis.[7]

De novo lesions

Overall, the evidence for the use of DEB in de novo lesions is scarce in the literature, compared to the data on its application intra-stent restenosis.

The Paclitaxel-Eluting PTCA-Balloon Catheter to Treat Small Vessel (PEPCAD I) was a multicenter non-randomized study that included 120 patients undergoing angioplasty with DEB (SeQuent Please™) and, when necessary, using BMS implantation for the de novo lesions measuring < 22 mm in leng thin small vessels (2.25-2.8 mm). The outcomes analyzed were late lumen loss at a 6 month angiographic evaluation (primary endpoint) and MACE and binary restenosis rates at 12 months (secondary endpoints). Patients treated with DEB had a more favorable outcome; with late lumen loss at 6 months of 0.16 ± 0.38 mm and restenosis rate of 6%, whereas those who required implantation of BMS had a luminal loss of 0.62 ± 0.73 mm and a restenosis rate of 45%. The MACE rates at 12 months were 6.1% for DEB and 37.5% for DEB + BMS, mainly due to the need for target lesion revascularization (5.0% vs. 28.0%; $p = 0.0005$).[24]

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Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels (PICCOLETO) was a randomized, open-label, non-inferiority study conducted in Italy, with the aim at comparing the results of angioplasty with a drug-eluting balloon (DIOR™, n = 29) and angioplasty with implantation of a DES (Taxus™, n = 28) in patients with stable or unstable angina and with *de novo* lesions in small-caliber vessels (≤ 2.75 mm). The primary endpoint was the stenosis rate on a 6 month angiographic assessment, and the secondary endpoints were binary restenosis and MACE at 9 months. The study was terminated after inclusion of two-thirds of the sample, due to the evident superiority of Taxus™ group, in which the stenosis rate was lower (43.6% vs. 24.3%; *p* = 0.029). Secondary endpoints also favored the DES group, with lower binary restenosis (32.1% vs. 10.3%; *p* = 0.043) and MACE (35.7% vs. 13.8%; *p* = 0.054) rates.[25]

Drug-Eluting Balloon in Bifurcation Utrecht (DEBIUT) was a prospective pilot study aimed to test the efficacy and safety of the DIOR™ DEB in 20 patients with *de novo* lesions in bifurcations. A DIOR™ balloon angioplasty was performed on the main and side branches and, when necessary, BMS were implanted in the main branch (19 stents/20 injuries). No stent was implanted in side branches. No MACE occurred within four months of follow-up. Angiographic data were not reported.[26]

Acute coronary syndromes

Besic et al.[27] conducted a single-center, prospective study to compare the approach of culprit lesions in patients in the setting of acute coronary syndromes without ST-segment elevation with BMS implantation, followed by a post-dilation with a drug-eluting balloon (Elutax™ in the first case, and SeQuent Please™ in subsequent cases; n = 44) vs. BMS implantation (n = 41). The outcomes assessed at 6 months were intra-stent restenosis and late lumen loss (primary endpoints), and the need for target lesion revascularization, stent thrombosis, and a new episode of acute coronary syndrome (secondary endpoints). The DEB + BMS group showed lower late lumen loss, 0.22 mm (0.00-2.35 mm) vs. 0.68 mm (0.00-2.15 mm), with *p* = 0.002; but there was no difference in binary restenosis (17.1% vs. 22.7%; *p* = 0.593) and MACE (24.4% vs. 29.5%, *p* = 0.835) rates. One patient in the DEB + BMS group had a subacute stent thrombosis.[27]

Drug-eluting Balloon in Acute ST-segment Elevation Myocardial Infarction (DEB-AMI) was a prospective, multicenter, randomized study aimed to compare angiographic, functional, and clinical outcomes of three strategies in the treatment of AMI with ST-segment elevation: BMS implantation, pre-dilation with DEB followed by BMS implantation (DEB + BMS), and DES implantation. 150 patients with less than 12 hours of symptoms, showing lesions in the culprit artery and with an antegrade flow restoration > Thrombolysis in Myocardial Infarction (TIMI 1), were included after thromboaspiration, without clinical and angiographic characteristics suggesting a high risk of restenosis. The outcomes analyzed were intra-stent late lumen loss (primary endpoint), and binary restenosis and MACE rates (secondary endpoints) at 6 months. The acute results of these procedures were similar between groups. In the late follow-up, obtained in 85% of patients, the primary endpoint, i.e., reduction of intra-stent late loss, was not achieved: 0.74 ± 0.57 mm in the BMS group vs. 0.64 ± 0.56 mm in the DEB + BMS group (*p* = 0.39). The late luminal loss in the DES group was significantly lower compared to the other two groups (0.21 ± 0.32 mm; all, *p* < 0.01). The same was noted in relation to binary restenosis (26.2% vs. 28.6% vs. 4.7%; *p* < 0.01) and MACE (23.5% vs. 20.0% vs. 4.1%, *p* = 0.02) rates. The analysis with optical coherence tomography showed stent strut malapposition in the DEB + BMS group and an even more significant malapposition in the DES group.[28] These data suggest that the use of DEB in pre-dilation of lesions during primary angioplasty brings no angiographic benefit to the routine implant procedure of BMS, not even in relation to the poor late apposition of the stent struts, with no reason for its application in this context.

Table 2 presents a summary of key clinical studies on DEBs.

RECOMMENDATIONS FOR DRUG-ELUTING BALLOONS IN CURRENT GUIDELINES

Currently, the European guideline for coronary revascularization[29] of 2014 recommends only the use of DEB for the treatment of intra-stent restenosis of BMS or DES (class I, level of evidence B). The American guideline[30] of 2011 has not issued any recommendations regarding these devices, due to lack of data allowing for formal recommendation for their use. The use of DEB in other clinical settings, for instance, *de novo* lesions or bifurcations, or small-caliber vessels, should be considered as an off-label indication.

CONCLUSIONS

Drug-eluting balloons are a promising technology in the arsenal of interventional cardiology devices, able to modulate neointimal proliferation, while avoiding the presence of platforms and polymers, responsible for vascular inflammation, which may lead to late deleterious consequences. However, the volume of data available in the literature on the effectiveness of these devices is still limited, since most of the information comes from studies on the treatment of intra-stent restenosis. Even in this field, published studies exhibit small samples, mostly considering substitutive outcomes, which do not allow for definitive conclusions. In other indications, the availability of literature data is still smaller, and its use is almost always the result of expert opinion.

TABLE 2
Major published clinical studies with drug-eluting balloon (DEB).

Study/year	Type	DEB	Groups	Scenario	n	Primary outcome	Results
PACCOCATH ISR I[16]	Randomized, multicenter	Paccocath™	DEB vs. balloon	Restenosis (BMS)	52	Late loss (at 6 months)	0.03 ± 0.48 vs. 0.74 ± 0.86 mm ($p = 0.002$)
PACCOCATH ISR I and II[18]	Randomized, multicenter	Paccocath™	DEB vs. balloon	Restenosis (BMS)	108	Late loss (at 6 months)	0.11 ± 0.45 vs. 0.81 ± 0.79 mm ($p < 0.001$)
PEPCAD II ISR[19]	Randomized, multicenter	SeQuent Please™	DEB vs. DES (Taxus™)	Restenosis (BMS)	131	Late loss (at 6 months)	0.17 ± 0.42 vs. 0.38 ± 0.61 mm ($p = 0.032$)
Habara et al.[20]	Randomized, multicenter	SeQuent Please™	DEB vs. balloon	Restenosis (DES, sirolimus)	50	Late loss (at 6 months)	0.18 ± 0.45 vs. 0.72 ± 0.55 mm ($p = 0.001$)
PEPCAD-DES[21]	Randomized, multicenter	SeQuent Please™	DEB vs. balloon	Restenosis (DES)	110	Late loss (at 6 months)	0.43 ± 0.61 vs. 1.03 ± 0.77 mm ($p < 0.001$)
ISAR-DESIRE[22]	Randomized, multicenter	SeQuent Please™	DEB vs. balloon vs. DES (paclitaxel)	Restenosis (DES, "limus")	402	Stenosis diameter (at 6 to 8 months)	DEB: 38% vs. DES: 37.4% (Pof non-inferiority = 0.007) vs. balloon: 54.1% (p of superiority < 0.0001)
RIBS V[23]	Randomized, multicenter	SeQuent Please™	DEB vs. DES (Xience™)	Restenosis of BMS	189	Minimal lumen diameter (at 9 months)	2.01 ± 0.6 vs. 2.36 ± 0.6 mm ($p < 0.001$)
PEPCAD I[24]	Register, prospective	SeQuent Please™	DEB	De novo lesions, vessels ≤ 2.75 mm	120	Late loss (at 6 months)	0.16 ± 0.38 mm
PICOLETTO[25]	Randomized, single-center	DIOR™	DEB vs. DES (Taxus™)	De novo lesions, vessels ≤ 2.75 mm	57	Stenosis percent (at 6 months)	43.6% vs. 24.3% ($p = 0.029$)
DEBIUT[26]	Pilot, prospective	DIOR™	DEB	Bifurcation lesions	20	Clinical events (at 4 months)	No occurrence
Besic et al.[27]	Randomized, single-center	Elutax™ and SeQuent Please™	BMS + post-dilation with DEB vs.BMS	ACS without ST elevation	85	Late loss (at 6 months)	0.22 (0.00-2.35) vs. 0.68 (0.00-2.15) mm ($p = 0.002$) 17.1% vs. 22.7% ($p = 0.593$)
DEB-AMI[28]	Randomized, multicenter	DIOR™	BMS vs. DEB + BMS vs.DES	AMI with ST elevation	150	Restenosis (at 6 months)	0.74 ± 0.57 vs. 0.64 ± 0.56 vs.0.21 ± 0.32 mm ($p < 0.01$)

BMS: bare metal stent; DES: drug-eluting stent; ACS: acute coronary syndrome; AMI: acute myocardial infarction.

CONFLICTS OF INTEREST

FUNDING SOURCES

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