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An Evaluation on Drug-Eluting Balloons in Arterial Circulatory Issues

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ABSTRACT

Endovascular interventions have recently become the first-line treatment for arterial diseases (AD). However, there is no consensus yet on the primary endovascular method. Intensive studies carried out in recent years have been aimed not only at the treatment of existing stenosis but also at preventing the narrowing problem. Drug-eluting balloons (DEB) have recently become a new alternative treatment in this context. DEB allows the release of antiproliferative drug into the stenosis area without leaving any stent strut. It increases the therapeutic effect by preventing intimal proliferation and restenosis. Available data show that DEB has satisfactory efficacy and low risk, is superior to BMS and is noninferior to DES. It may be a suitable alternative for preventing coronary and peripheral artery diseases and in-stent stenosis.

This article aims to review current data on the use of DEB in arterial diseases.

Keywords

Arterial diseases, Atenosis, In-stent stenosis, Drug-eluting balloons.

Introduction

Arterial diseases (AD) pose a significant burden on healthcare systems [1]. If left untreated, they are associated with significant mortality and morbidity, including cardiac events and stroke [2]. Endovascular interventions have recently become the first-line treatment for AD and are performed on millions of people worldwide each year [2,3]. A variety of endovascular intervention techniques are currently available, including plain or drug-eluting balloons, bare metal, or drug-eluting stents [4-7]. However, there is no consensus on which method should be given priority [8].

Vascular stenosis requiring endovascular intervention remains a significant clinical problem. The mechanisms that lead to stenosis are complex and not yet fully understood [9,10]. In addition, natural stenosis and intervention-induced stenosis are significantly different in terms of their formation mechanisms [11]. While intimal hyperplasia, which causes stenosis by thickening the vessel wall, usually takes several years in the native atherosclerosis, the intervention-induced stenosis usually occurs in a shorter time after endovascular intervention [12].

Intensive efforts made in recent years have been directed not only to the treatment of existing stenosis but also to prevent the problem of restenosis. As a result of these initiatives to reduce restenosis, the rate of restenosis has been significantly reduced, especially with the use of drug-eluting stents (DES) [4,7]. However, restenosis still remains a problem, and drug-eluting balloons (DEB) have recently become a new treatment strategy both in this context and for arterial structures with different characteristics [3,13,14].

The aim of this article is to review the current data regarding the use of DEB in arterial narrowing with different clinical situations.

Reality Regarding the Use of DEB in Arterial Stenosis

The main events in arterial narrowing are the formation of neointimal hyperplasia and neo-atherosclerosis due to migration and proliferation of inflammatory cells and vascular smooth muscle cells (VSMCs) [15]. Although plain balloon angioplasty

has been found effective in providing patency of vascular stenosis, the artery re-narrows at a high rate (32-55%) in the early period, primarily due to the shaping/elastic rebound mechanism [16]. Despite significant improvement, stenosis due to metal contact-related stent thrombosis or in-stent restenosis continued to occur with rates of 17-41% and up to 10% with BMS use and DES use, respectively [7,11,16].

DESs aim to prevent the formation of neointimal hyperplasia with special antiproliferative drugs (sirolimus, paclitaxel, etc.) coated on them. Although it prevents restenosis significantly, the problem is not still negligible, especially in the long-term outcomes are poor due to the left stent material [4]. DEB is a new endovascular intervention technique that combines balloon angioplasty and drug release technology, used in cases of both new stenosis and restenosis of blood vessels [14]. DEB allows the application of antiproliferative drug to the area of stenosis, without leaving an additional layer of stent strut [17]. Its use is increasing due to its good therapeutic effect in preventing intimal proliferation and restenosis [18].

DCB consists of three main components: active ingredient, excipient and balloon [13]. These components are combined to meet clinical requirements such as sustained drug delivery at therapeutic doses, long-term maintenance of drug concentration in blood vessel walls, and low or no toxicity to the body [19]. During expansion of the balloon, excipients both bind the drug to the endothelium and mucus layer and ensure stability before gradual controlled release, making long-term treatment possible [8].

Following adequate preliminary dilatation, a balloon-vessel ratio of 0.8-1.0/1.0 is recommended, DEB are deployed to expand the narrowed vessel. During the deployment, the drug is released from the balloon and allowed to reach the lesion and penetrate the vessel wall [8,20]. This drug release shows an inhibitory effect on intimal hyperplasia. The excipient (such as urea, iopromide, tributyl acetyl citrate and polyester-based polymers) facilitates the release and transfer of the drug to the target lesion [17].

Paclitaxel is used as an antiproliferative drug in some commercial DEBs (including Extender PTCA, IN.PACT Falcon, Essential), while sirolimus and its derivatives are used in others (including Virtue, Selution) [3]. Paclitaxel is more lipophilic and has faster cellular uptake. However, based on existing clinical studies, no evidence of a "class effect" of different DEBs has been shown [5,21].

Drug Eluting Balloons in the Treatment of Arterial Diseases

DEB is one of the cutting-edge technologies developed as a new clinical treatment method for both native coronary and peripheral artery diseases and the in-stent restenosis after their stenting. It has a better long-term treatment effect than DEB, BMS and DES techniques, especially in the treatment of coronary artery disease [13]. Since DEB can be used alone or in combination with BMS, it offers advantages such as uniform drug delivery to the vascular wall, absence of metallic foreign body residue, shortening the duration of antiplatelet therapy, and reducing restenosis rates [8,20,22]. One of the key features of DEB alone angioplasty is late lumen expansion (LLE) [23].

DEB in coronary arterial diseases

In large coronary artery disease

Large coronary arteries (≥2.8 mm) include the right coronary artery, the left anterior descending branch, and the left circumflex branch. Lesions in these vessels may present as diffuse, obstructive, or bifurcation lesions, highlighting widespread involvement of large vessels. As a result, the investigation and treatment of large coronary arteries faces numerous vascular limitations [13]. Although limited data are available, studies show that the rate of late adverse cardiovascular events in the large vessel lesion group is lower in groups treated with DEB than DES [13,24]. Current evidence suggests that DEB may be a safe and effective alternative in the treatment of large coronary artery disease.

In Small Coronary Artery Disease

Currently, the lack of stents suitable for clinical use makes small coronary artery (<2.8 mm) disease a major concern in clinical practice in terms of technical implications and restenosis [13]. Approximately 40-50% of coronary lesions occur in small arteries, and 30-50% of coronary interventions are directed towards these lesions [25]. Several studies have shown that patients using DEB have lower rates of restenosis, adverse cardiac events, and late lumen loss than those using DES, and that DEB treatment is no less effective than DES treatment [8,26,27].

In Coronary Artery Bifurcation Lesion

Coronary artery bifurcation lesions are a common form of coronary artery disease. The use of balloons in the treatment of bifurcation lesions attracts attention [13]. The effectiveness of DEBs has been demonstrated in the treatment of bifurcation lesions of both collateral and main coronary arteries. Additionally, when combined with directional coronary atherectomy, positive clinical outcomes can be achieved with minimal branch damage [28]. This makes it a potential stent-free percutaneous coronary intervention strategy. Some consensus groups have proposed the feasibility of percutaneous coronary intervention as a treatment method for coronary bifurcation disease [28,29].

DEB in peripheral arterial diseases

In femoropopliteal artery disease

Among the peripheral arteries, the femoral popliteal artery is the most commonly affected by atherosclerotic conditions [30]. Conventional interventional treatments of PAD are associated with a high rate of restenosis [13]. Studies have shown that DEBs exhibit advantages over traditional angioplasty and DES [31,32]. The findings of these studies suggest that DEBs offer an alternative approach to increase patency and reduce the risk of restenosis in femoropopliteal artery disease.

In Renal Artery Disease

The renal artery is frequently subjected to stenosis due to reasons such as primarily atherosclerotic stenosis and then aortitis and

myofibrillar dysplasia of the artery wall. Stent placement in the renal artery may cause mechanical damage, resulting in intima disruption and subsequent ISR [13,33]. DEBs have the potential to reduce antiplatelet drug use and alleviate the inflammatory response [34,35].

DEB in-stent restenosis

ISR is the initial indication for use of DCB. The current European guidelines recommend both DES and DEB with Class I indication for the treatment of ISR [5]. Current study data show that DES and DEB are the most superior and second most superior techniques, respectively, among endovascular methods in the treatment of ISR [36-38]. At long-term follow-up, DEB therapy appeared to be moderately less effective than repeated DES in reducing TLR in patients with coronary DES-ISR [36]. Late lumen loss (LLL) even appears to be slightly lower in the DEB arm compared to DES [36,37].

The underlying mechanism in ISR is primarily the long-term presence of the metallic stent as a foreign body within the arterial vascular system. This metallic entity can cause neointimal hyperplasia and ultimately in-stent restenosis [13]. In these cases, DEB, which does not leave a metallic residue, offers an alternative approach [39].

Discussion and Conclusion

Since the first use of DCBs for ISR in 2003, they have been shown to significantly reduce late lumen loss compared to uncoated BA [36,42,43]. DCB has been recommended for use in the treatment of small vessel disease and ISR due to its effectiveness and safety, such as reducing the risk of in-stent restenosis and late in-stent thrombosis and even causing late lumen expansion [47]. These successes have led to the application of DEBs for new indications such as bifurcation lesions and large artery lesions and to further research in this field [8,23,25].

DCB has a number of advantages. First, no foreign body is implanted into the patient's body during DEB angioplasty, which prevents complications such as late stent thrombosis and allergies. Secondly, the interventional procedure has a shorter operating time and therefore less radiation exposure for medical personnel and patients. Again, DCB reduces the risk of delayed reendothelialization by ensuring that the drug can be delivered evenly to the inner wall of the blood vessel. Importantly, it reduces the risk of bleeding and other complications because it shortens the duration of dual antiplatelet therapy. Finally, it may be more suitable than stenting for special situations such as narrow lesions and high bleeding risk lesions [47].

A significant number of trials and studies are currently ongoing to find further answers regarding the feasibility of DEB as an alternative to DES, including REVERSE trial (ClinicalTrials.gov: NCT05846893) for large coronary artery diseases, TRANSFORM I trial (ClinicalTrials.gov: NCT 03913832) for small coronary artery

Table 1: Some study examples comparing DEB with other treatments in the treatment of in-stent restenosis.

Comparison arm	Treatment History	Follow-up		Study (Ref.)
		Outcomes	Follow-up time (months)	
PB	BMS	-LLL: 0,03±0,48 mm vs. 0,74±0,86 mm (p=0.002) -MACE: 4% vs. 31% (p=0.01)	12	Scheller et al. [40]
DES-P	DES	-LLL: 0,46±0,51 mm vs. 0,55±0,61 mm (p<0.001) -TLF: 17% vs. 16% (p=0.52)	12	PEPCAD China ISR [41]
DES-E	BMS	-MLD: 2.01±0.60 mm vs. 2.36±0.60 mm (p<0.001) -MACE: 8% vs. 6% (p=0.60)	12	RIBS V [42]

Abbreviations: DEB, drug-eluting balloon; PB, plain; DES-P, paclitaxel-coated drug-eluting stent; DES-E, 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: Some study examples comparing DEB with other treatments in the treatment in large and small coronary artery diseases.

Comparison arm	Follow-up		Study (Ref.)
Large coronary artery disease (≥2.8 mm)			
BMS	MACE (1% vs 14% (p<0.001)	9 months	DEBUT [43]
DES	-MACE (4% vs 5.6% (p<0.65) -TLR (2.4% vs 3.2% (p=0.6)	12 months	Jiang et al. [44]
Small coronary artery disease (<2.8 mm)			
DES	- TVR (3.5% vs 4.5% (p=0.44) - MACE (7.5% vs 7.3% (p=0.92)	12 months	BASKET-SMALL 2 [17]
DES	- TLF (4.4% vs 2.6% (p=0.72)	9 months	RESTORE-SVD China [45]
PB	-13.3% vs 42.5% (p<0.01) -TLR (3.4% vs 10.3% (p=0.2)	6 months	Funatsu et al. [46]

diseases, DCB-HBR trial (ClinicalTrials.gov: NCT 05221931) for high blood risk lesions, ISAR-DESIRE5 trial (ClinicalTrials.gov: NCT 05544864) for difference in neointima formation pattern.

DCB has the potential to overcome the limitations of DES safely and efficiently and to be an important alternative in arterial lesions with different anatomical locations and various clinical features. Overall, it has satisfactory efficacy and low risk with superiority to BMS and noninferiority to DES, as well as lower late lumen loss. Numerous clinical studies have been conducted demonstrating its safety and effectiveness in treating various coronary and peripheral artery diseases and preventing in-stent stenosis. However, more studies are needed. In this sense, ongoing research with different clinical designs and the development of new drugs and technologies may help us more in the optimal use of DCB in the coming years.

Conflicts of Interest

RD is the president of Invamed (Ankara, Turkey).

References

1. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010 a systematic review and analysis. Lancet. 2013; 382: 1329-1340.
2. Gerhard-Herman MD, Gornik HL. Writing Committee Members. AHA/ACC Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease Executive Summary. Vasc Med. 2016; 22: NP1-NP43.
3. Ge JB, Chen YD. Expert Writing Committee of the Chinese Expert Consensus on Clinical Applications of Drug-Coated Balloon Chinese expert consensus on the clinical application of drug-coated balloon. J Geriatr Cardiol. 2024; 21: 135-152.
4. Scafa Udriște A, Niculescu AG, Grumezescu AM, et al. Cardiovascular Stents A Review of Past Current and Emerging Devices. Materials Basel. 2021; 14: 2498.
5. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European heart journal. 2019; 40: 87-165.
6. Vahabli E, Mann J, Heidari BS, et al. The Technological Advancement to Engineer Next-Generation Stent-Grafts Design Material and Fabrication Techniques. Adv Healthc Mater. 2022; 11: e2200271.
7. Canfield J, Totary-Jain H. 40 Years of Percutaneous Coronary Intervention History and Future Directions. J Pers Med. 2018; 8: 33.
8. Jeger RV, Eccleshall S, Wan Ahmad WA, et al. Drug-Coated Balloons for Coronary Artery Disease Third Report of the International DCB Consensus Group. JACC Cardiovasc Interv. 2020; 13: 1391-1402.
9. Clare J, Ganly J, Bursill CA, et al. The Mechanisms of Restenosis and Relevance to Next Generation Stent Design. Biomolecules. 2022; 12: 430.
10. Yahagi K, Kolodgie FD, Otsuka F, et al. Pathophysiology of native coronary vein graft and in-stent atherosclerosis. Nat Rev Cardiol. 2016; 13: 79-98.
11. Nusca A, Viscusi MM, Piccirillo F, et al. In Stent Neo-Atherosclerosis Pathophysiology Clinical Implications Prevention and Therapeutic Approaches. Life Basel. 2022; 12: 393.
12. Dinc R. Post-Stenting Restenosis in Coronary Artery Diseases Pathophysiology and Morphological Features of Re-Stenotic Tissue. J Sci Tech Res. 2023; 53: 44836-44841.
13. Lu K, Ye X, Chen Y, et al. Research progress of drug eluting balloon in arterial circulatory system. Front Cardiovasc Med. 2024; 11: 1287852.
14. Lazar FL, Onea HL, Olinic DM, et al. A 2024 scientific update on the clinical performance of drug-coated balloons. Asia Intervention. 2024; 10: 15-25.
15. Dinc R. A review of the current state in neointimal hyperplasia development following endovascular intervention and minor emphasis on new horizons in immunotherapy. Transl Clin Pharmacol. 2023; 31: 191-201.
16. Buccheri D, Piraino D, Andolina G, et al. Understanding and managing in-stent restenosis a review of clinical data from pathogenesis to treatment. J Thorac Dis. 2016; 8: E1150-E1162.
17. Jeger RV, Farah A, Ohlow MA, et al. Drug-coated balloons for small coronary artery disease BASKET-SMALL 2 an open-label randomised non-inferiority trial. Lancet. 2018; 392: 849-856.
18. Yeh RW, Shlofmitz R, Moses J, et al. Paclitaxel-Coated Balloon vs Uncoated Balloon for Coronary In-Stent Restenosis The AGENT IDE Randomized Clinical Trial. JAMA. 2024; 331: 1015-1024.
19. Gertz ZM, Wilensky RL. Local drug delivery for treatment of coronary and peripheral artery disease. Cardiovasc Ther. 2011; 29: e54-e66.
20. Bukka M, Rednam PJ, Sinha M. Drug-eluting balloon design technology and clinical aspects. Biomed Mater. 2018; 13: 032001.
21. Yerasi C, Case BC, Forrestal BJ, et al. Drug-Coated Balloon for De Novo Coronary Artery Disease JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75: 1061-1073.
22. Januszek R, Bil J, Gilis-Malinowska N, et al. Long-term outcomes following drug-eluting balloon or thin-strut drug-eluting stents for treatment of in-stent restenosis stratified by duration of dual antiplatelet therapy DEB-Dragon Registry. Advances in Interventional Cardiology. Postepy Kardiol Interwencyjnej. 2022; 18: 14-26.
23. Kleber FX, Schulz A, Waliszewski M, et al. Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. Clin Res Cardiol. 2015; 104: 217-225.
24. Yu X, Ji FS, Xu F, et al. Efficacy of paclitaxel coated balloon in the treatment of primary coronary artery lesions with a diameter of 2.8 mm and above. Chin J Cardiovasc Dis. 2018; 46: 32-38.

25. Megaly M, Saad M, Brilakis ES. Role of drug-coated balloons in small-vessel coronary artery disease. USC. 2019; 13: 16-20.

26. Latib A, Colombo A, Castriota F, et al. A randomized multicenter study comparing apaclitaxel drug-eluting balloon with a paclitaxel-eluting stent in small coronary vessels the BELLO Balloon Elution and Late Loss Optimization study. J Am Coll Cardiol. 2012; 60: 2473-2480.

27. Cortese B, Di Palma G, Guimaraes MG, et al. Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease: PICCOLETO II Randomized Clinical Trial. JACC Cardiovasc Interv. 2020; 13: 2840-2849.

28. Piraino D, Cortese B, Buccheri D, et al. Healing after coronary artery dissection The effect of a drug coated balloon angioplasty in a bifurcation lesion. A lesson from intravascular ultrasound analysis. Int J Cardiol. 2016; 203: 298-300.

29. Burzotta F, Lassen JF, Lefèvre T, et al. Percutaneous coronary intervention for bifurcation coronary lesions the 15th consensus document from the European Bifurcation Club. Euro Intervention. 2021; 16: 1307-1317.

30. Dinc R. Endovascular Treatment Strategies of Lower Extremity Peripheral Artery Disease An Overall Assessment in Terms of Cost and Effectiveness. J Anesth Surg. 2023; 9: 1-7.

31. Liistro F, Angioli P, Porto I, et al. Drug-Eluting Balloon Versus Drug-Eluting Stent for Complex Femoropopliteal Arterial Lesions: The DRASTICO Study. J Am Coll Cardiol. 2019; 74: 205-215.

32. Bausback Y, Wittig T, Schmidt A, et al. Drug-Eluting Stent Versus Drug-Coated Balloon Revascularization in Patients With Femoropopliteal Arterial Disease. J Am Coll Cardiol. 2019; 73: 667-679.

33. Moussa ID, Mohananey D, Saucedo J, et al. Trends and Outcomes of Restenosis After Coronary Stent Implantation in the United States. J Am Coll Cardiol. 2020; 76: 1521-1531.

34. Takahashi EA, McKusick MA, Bjarnason H, et al. Treatment of In-Stent Restenosis in Patients with Renal Artery Stenosis. J Vasc Interv Radiol. 2016; 27: 1657-1662.

35. Morosetti D, Chiocchi M, De Crescenzo F, et al. Bilateral renal artery stenosis treated with drugeluting balloon angioplasty in unique treatment. Radiol Case Rep. 2018; 14: 242-245.

36. Giacoppo D, Alfonso F, Xu B, et al. Drug-Coated Balloon Angioplasty Versus Drug-Eluting Stent Implantation in Patients with Coronary Stent Restenosis. J Am Coll Cardiol. 2020; 75: 2664-2678.

37. Ma Z, Liu K, Hu Y, et al. Comparison Between Drug-Coated Balloon and Stents in Large De Novo Coronary Artery Disease A Systematic Review and Meta-Analysis of RCT Data. Cardiovasc Drugs Ther. 2024.

38. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis a network meta-analysis. Lancet. 2015; 386: 655-664.

39. Chaabane C, Otsuka F, Virmani R, et al. Biological responses in stented arteries. Cardiovasc Res. 2013; 99: 353-363.

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

41. Xu B, Gao R, Wang J, et al. A prospective multicenter randomized trial of paclitaxel-coated balloon versus paclitaxel-eluting stent for the treatment of drug-eluting stent in-stent restenosis results from the PEPCAD China ISR trial. JACC Cardiovasc Interv. 2014; 7: 204-211.

42. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis the RIBS V Clinical Trial Restenosis Intra-stent of Bare Metal Stents paclitaxel- eluting balloon vs. everolimus-eluting stent. J Am Coll Cardiol. 2014; 63: 1378-1386.

43. Rissanen TT, Uskela S, Eränen J, et al. DEBUT trial investigators. Drug-coated balloon for treatment of de-novo coronary artery lesions in patients with high bleeding risk DEBUT a single-blind randomized non-inferiority trial. Lancet. 2019; 394: 230-239.

44. Jiang JL, Huang QJ, Chen MH. Efficacy and safety of drug-coated balloon for de novo lesions of large coronary arteries Systematic review and meta-analysis of randomized controlled trials. Heliyon. 2024; 10: e25264.

45. Tang Y, Qiao S, Su X, et al. Drug-Coated Balloon Versus Drug-Eluting Stent for Small-Vessel Disease The RESTORE SVD China Randomized Trial. JACC Cardiovasc Interv. 2018; 11: 2381-2392.

46. Funatsu A, Nakamura S, Inoue N, et al. A multicenter randomized comparison of paclitaxel-coated balloon with plain balloon angioplasty in patients with small vessel disease. Clin Res Cardiol. 2017; 106: 824-832.

47. Wang L, Li X, Li T, et al. Novel application of drug-coated balloons in coronary heart disease A narrative review. Front Cardiovasc Med. 2023; 10: 1055274.