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The evolution of percutaneous coronary intervention: past, present, future

Razvoj perkutane koronarne intervencije: preteklost, sedanjost, prihodnost

Tadej Žlahtič, Luka Vitez, Matjaž Bunc

Abstract

Interventional cardiology has, from the first femoral coronary angioplasty in year 1977, significantly improved therapy of ischaemic heart disease. During this time, plain old balloon angiography has transformed into an adjunctive method of target lesion preparation and optimization. The development of bare metal stents has improved outcomes by reducing elastic recoil, injury and constrictive remodellation of coronary arteries. Further, the evolution of antiaggregation therapy has reduced the incidence of stent thrombosis. Even though accomplishments were significant, new challenges have emerged. Clinical studies have indicated the importance of neointimal hyperplasia in in-stent restenosis and showed us possible pharmacological targets. This led to the development of modern drug-eluting stents with the use of antiproliferative drugs, which further reduced adverse outcomes. However, they still represent an artificial material and thus promote chronic inflammation, neo-atherosclerosis and therefore restenosis and very late stent thrombosis. With this in mind, the latest technological breakthroughs have been intensively focused on the so-called leave- nothing-behind strategies. One of the most promising future therapeutic possibilities, beside bioresorbable stents, is drug eluting balloon. It enables dilatation of coronary arteries and delivery of an antiproliferative drug to the target lesion without the use of scaffold that would promote inflammation and neo-atherosclerosis.

Izvleček

Od prve koronarne angioplastike leta 1977 preko femoralnega pristopa je intervencijska kardiologija drastično spremenila zdravljenje ishemične bolezni srca. Prvotna perkutana transluminalna angioplastika z uporabo navadnih balonskih katetrov je sčasoma postala le pomožna tehnika za pripravo žilne spremembe in optimiziranje vstavljene žilne opornice. S pojavom navadnih žilnih opornic smo izboljšali rezultate na račun zmanjšanega elastičnega odsunka, poškodbe in konstriktivnega remodeliranja koronarnih arterij, z razvojem antiagregacijske terapije pa dosegli manjše število tromboz v žilnih opornicah. Ob nadaljnjih raziskavah neointimalne hiperplazije so se pojavile metode za lokalno apliciranje antiproliferacijskih zdravil. Razvile so se z zdravili prevlečene opornice, ki so leta 2019 postale novi zlati standard. Ob uporabi

Department of Cardiology, Division of Internal Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia

Correspondence / Korespondenca: Tadej Žlahtič, e: tadej.zlahtic@gmail.com

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Ključne besede: angioplastika; z zdravili prevlečene opornice; koronarne; baloni/trendi; prevlečeni materiali

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modernejših materialov so poskrbele za izboljšanje rezultatov na račun zmanjšanja neointimalne hiperplazije in števila zapletov. A kljub temu so še vedno tujek v žilni steni, ki spodbuja kronično vnetje, neoaterosklerozo, s tem pa restenozo ter zelo pozne pojave tromboze. To spoznanje zadnja leta vodi v razvijanje tehnik, ki bi za sabo pustile čim manj tujega materiala oziroma bi bil le-ta čimbolj biološko kompatibilen. Ob razvoju razgradljivih žilnih opornic so ena obetajočih terapevtskih možnosti z zdravili prevlečeni balonski katetri, ki razširijo žilno svetlino in lokalno aplicirajo antiproliferativno zdravilo na samo mesto spremembe brez uporabe opornice, ki bi ostala v žilni steni in spodbujala vnetje.

1 Introduction

The beginnings of cardiac catheterization and thus interventional cardiology date back to 1711, when Stephen Hales measured the blood pressure in the ventricles of a horse's heart for the first time. With further development of physiology, catheterization methods and related technologies, interventional cardiology began to flourish in the 20th century. It was in the first half of the century, after the first successful catheterizations of the right side of the heart, that the importance and potential of the newly discovered method were determined. On this account, the Nobel Prize in Physiology and Medicine (Cournand, Richards and Forssmann) was awarded in 1956. The next important turning point was the first coronary angiography performed in 1967 via the femoral approach (1). Catheterization methods then drastically changed the treatment and diagnosis of ischemic heart disease. In Slovenia, the first urgent percutaneous coronary revascularization was performed in 1989 in a patient with an acute ST-elevation myocardial infarction (2). With the development of the method and important advantages over the systemic thrombolysis used at that time, percutaneous coronary intervention became established in Slovenia as well. In 2000, the University Medical Centre Ljubljana thus introduced an uninterrupted intervention service to provide access to the urgent diagnosis and treatment of acute coronary syndrome 24 hours a day, 7 days a week (2,3). Despite rapid and successful progress, new improvements and developments are already being witnessed. Newer materials, drugs, and attractive techniques make it possible to repair and maintain a satisfactory blood flow through the coronary arteries with minimal invasiveness and without permanent insertion of artificial materials. The foreign literature calls these procedures the "*leave-nothing-behind*" strategy.

This article will present the development of current methods in percutaneous coronary intervention (PCI). Through percutaneous transluminal angioplasty using plain old balloons (POBA), bare metal stents (BMS) and drug-eluting stents (DES), we will demonstrate the usefulness of developing and using drug-eluting balloons (DEB).

2 Percutaneous transluminal angioplasty using plain old balloons

The rapid development of PCI began in 1977 when Grüentzig and Myler carried out the first percutaneous angioplasty using a conventional balloon catheter (1,4,5). Balloon catheters, that were initially non-compliant and usable only at relatively low pressures, changed significantly over the next ten years, with a simultaneous development of delivery methods.

POBA uses compliant, semi-compliant or non-compliant balloon elements to resolve vascular stenosis. They work by causing the vascular wall to stretch excessively with pressure, leading to iatrogenic micro- and macrodissections (6). This mechanism was also the reason for many restrictions. Upon extension, endothelium was damaged in 3–8% and dissections with acute thrombotic obstruction occurred. However, if there were no dissections, subacute obstructions due to elastic recoil were recorded in 5–10% of patients. This occurred after the cessation of the balloon force effect without damage to the vessel wall. Damage to the vascular wall also caused necrosis of the smooth muscle cells of the media, which stimulated their proliferation and migration into the intima (neointimal hyperplasia). This led to frequent restenosis in the first six months after the procedure (30–50% of restenosis detected by angiography) (4,6,7). Later, using intravascular ultrasound, it was found that not only neointimal hyperplasia but also negative vascular remodelling due to fibrosis contributed to restenosis (6,8). All these complications and their frequent presentation in the community of experts have encouraged the search for new solutions to reduce both early and late complications.

We currently know a number of compliant, semi-compliant and non-compliant balloon catheters of various lengths, diameters and inflation pressure loads.

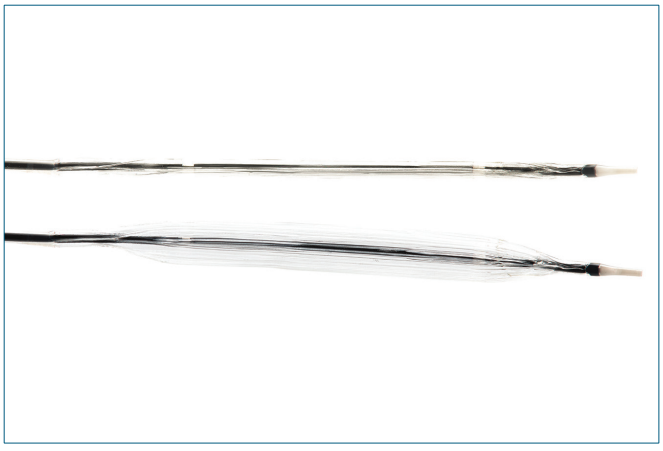

Figure 1: Europa Ultra semi-compliant balloon (Rontis medical, Zug, Switzerland). In folded (below) and unfolded state (above). Images from our own archive.

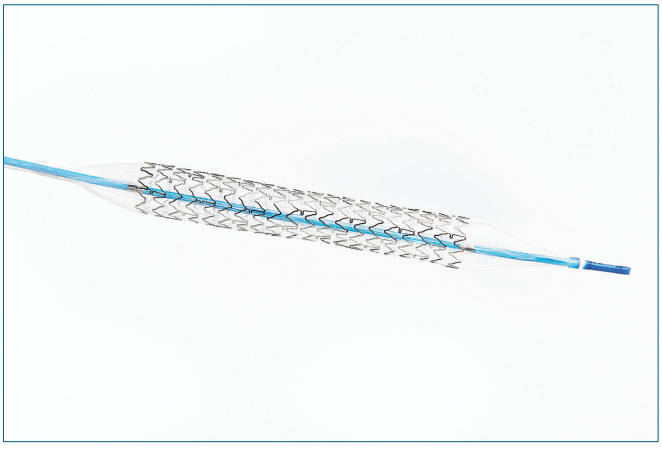

Figure 2: Expanded BMS mounted on carrying balloon. The original POBA enabled the delivery and development of vascular stents. Multi-Link Vision BMS (Abbott, Illinois, USA). Images from our own archive.

Semi-compliant and compliant balloon catheters (Figure 1) increase their volume by increasing pressure. The nominal diameters are reached at the pressure specified by the manufacturer. As the pressure increases above the nominal, they expand continuously. However, the flexibility of the balloon element causes an uneven distribution of forces on the vessel wall. Non-compliant balloon catheters expand more evenly, their diameter increases relatively little with the increase above nominal pressure, and the forces, as they expand, are evenly distributed along the narrowed part (5). In addition to the classic POBA, balloon catheters with metal or plastic surface elements have also been developed to reduce the number of complications and to treat more severe lesions. These elements, when stretched, apply forces in a targeted way and enable controlled damage to the vessel. Cutting balloons perform this by incising the vessel wall. This allows the vessel to dilate with less pressure, more controlled dissection and thus less damage. The result is a smaller inflammatory and proliferative response in the vessel wall. Scoring balloons have a similar mechanism with targeted application of forces. Unfortunately, studies have not shown a reduction in restenosis and greater clinical advantages over classical POBA (5,9). They have gained their place mainly in resolving calcified lesions, in which they have been overtaken in recent years by the development of intravascular lithotripsy with Shockwave balloon catheters (Shockwave Medical Inc., Fremont, California, USA). Roughly speaking, we can call it an upgrade of the POBA technique using electrical elements in a balloon around the supporting system. When connected to the external power supply unit, they generate an electrical pulse that gasifies the liquid in the balloon. The resulting microscopic bubbles create a pressure wave. This spreads at a higher rate in solids than in soft substances, which is why calcinations gradually break down (10,11). The safety of the method has been demonstrated by the DISRUPT CAD I and II studies, and the DISRUPT CAD III study is currently underway (12).

The current use of POBA is mainly limited to the preparation of the vascular lesion before the insertion of the vascular stent (predilatation) and the optimization of the inserted vascular stent (postdilatation). Balloon catheters with higher compliance are mostly used for predilatation, while high-pressure non-compliant balloon catheters are preferred in postdilatation (6). In difficult calcinations, the use of advanced balloon catheters with different characteristics is also possible.

3 Percutaneous transluminal angioplasty using vascular stents

Due to the relatively large number of complications in POBA, in the following years, the concept of metal meshes began to emerge, which would prevent vessel recoil, negative remodelling and close the edges of dissections in case of vascular damage, thus reducing the incidence of thrombosis and restenosis (Figure 2). The first BMSs made of stainless steel were created, which were the basis for later stents made of newer materials (Table 1) and DESs (4,13). Initially high incidences of in-stent thrombosis, in as many as 25% of cases within 14 days after BMS insertion, decreased to less than 1% with the development of antiaggregation therapy and the use of high expansion pressures. At the same

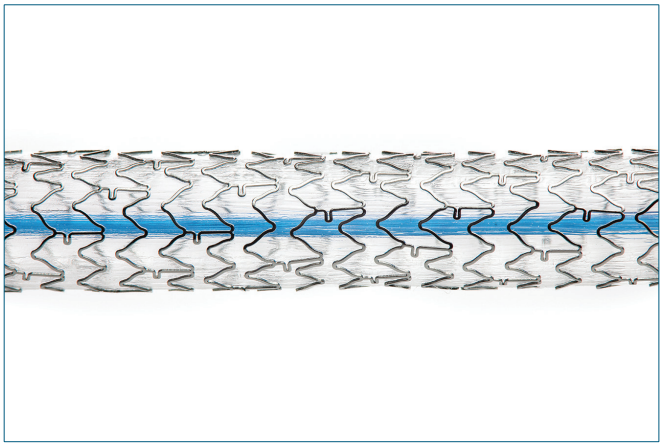

Figure 3: Multi-Link Vision BMS (Abbott, Illinois, USA). Stent representative with laser-cut slots from a single cobalt-chromium tube with a supported cell geometry. The stent is expanded on carrying balloon. Images from our own archive.

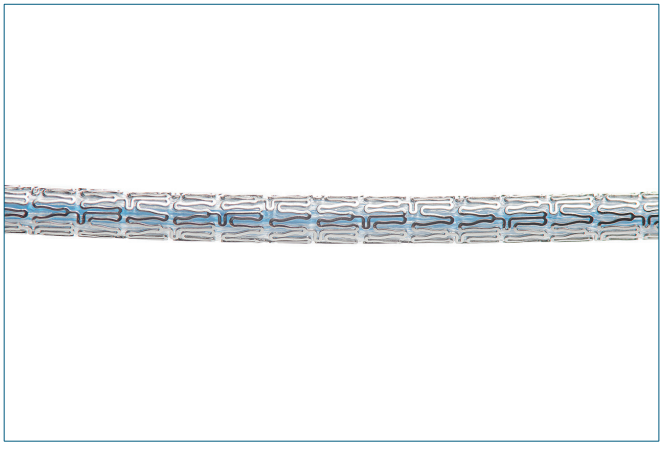

Figure 4: Multi-Link Vision BMS (Abbott, Illinois, ZDA). Unexpanded stent on carrying balloon. Images from our own archive.

time, better angiographic results were observed due to reduced elastic recoil of the vessel, closure of dissections and dissected plaques, and reduction of constrictive remodelling of coronary arteries (5,14). As proof of the efficacy and safety of the new method compared to POBA, two major revolutionary studies were conducted in the mid-1990s, namely the European Belgium-Netherlands Stent trial (BENESTENT) and the North American Stent Restenosis Study (STRESS) (7). BENESTENT showed superiority of BMS compared with POBA based on the better angiographic score (higher minimum lumen in control coronary angiography) and lower incidence of restenosis (proportion of re-identified stenoses ≥ 50%) (13). The similarly conducted STRESS study, just like BENSTENT, demonstrated the superiority of BMS (4,15).

The development led to the use of newer, stronger cobalt-chromium and platinum-chromium alloys, which enabled the fabrication of thinner structures with different architectures. According to the shape of the framework, the stents are divided into coil stents, tubular mesh stents, tubular slotted stents (Figures 3 and 4), and modular stents. Coil stents did not work due to poor resistance. Tubular slotted stents with slits did better. They had more radial force, but at the expense of less flexibility and deliverability to the site of lesion. They were replaced by modular structures that excel in flexibility and possible access to side branches. There are also different shape subtypes according to the use of closed (Figures 5 and 6) and open cells and shapes of structural elements of stents in cross section (Figures 3 and 4). All this leads to significant differences in the delivery of stents to the site of the target lesion, in flexibility and the resistance to radial forces. Despite all efforts and more modern shapes, in-stent restenosis (ISR) has remained an important late complication. As much as 20–40% of all PCIs were performed on account of ISR in BMS (4,7,16-19).

Intervention with BMS represented a major step towards resolving complications due to elastic recoil, injury, and constrictive remodelling of coronary arteries. In addition, the development of dual antiaggregation therapy has reduced the number of thromboses in vascular stents. With studies of neointimal hyperplasia and numerous unsuccessful studies with systemic pharmacological agents that initially showed possible grips for ISR reduction in *in vitro* and animal models, development has been limited to the local delivery of antiproliferative drugs. DES has been developed (5,14,20).

4 Percutaneous transluminal angioplasty using drug-eluting stents

The first generation of DES contained a framework coated with a polymer that acted as a reservoir of paclitaxel (Taxus® stent), a microtubule inhibitor or sirolimus (Cypher® stent), an mTOR inhibitor. Both were selected for their pronounced antiproliferative and anti-inflammatory properties, which reduce neointimal proliferation (4,14). The SIRIUS and TAXUS studies showed the safety of DES and lower revascularization needs due to ISR, with statistically significant results (21,22). With their increased use, however, limitations have also emerged. Due to the inhibition of proliferation, endothelialisation in the area of the inserted DES

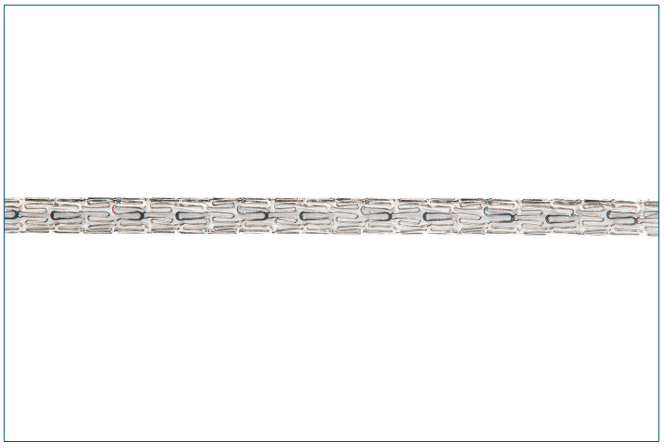

Figure 5: EluNIR Ridaforolimus DES (Medinol, Tel Aviv, Israel), laser-cut from a cobalt-chromium plate, with elastomeric coating with ridaforolimus, welded into a tube with WiZeCell cell architecture (Medinol, Tel Aviv, Israel), a hybrid between open and closed architecture. Unexpanded on carrying balloon. Images from our own archive.

Figure 6: EluNIR Ridaforolimus DES (Medinol, Tel Aviv, Israel). Expanded. Images from our own archive.

Figure 7: EluNIR Ridaforolimus DES (Medinol, Tel Aviv, Israel) during expansion. Visible metal tip on the delivery system for easier delivery to the lesion site. Images from our own archive.

was prolonged. Along with the inflammatory response, allergic reaction to the used artificial materials and neo-atherosclerosis, this led to a late stent thrombosis. These were still visible more than one year after their insertion despite appropriate antiaggregation therapy (14). The high incidence and mortality due to thrombosis challenged the leading role of DES in the catheter laboratory. In response, a second generation was developed (Table 1) with everolimus and zotarolimus, both more lipophilic and tissue-permeable with less loss upon contact with blood. The metal basis of the stent was made of cobalt-chromium (Figures 5 and 6) and platinum-chromium alloy. This reduced the diameter of the structural elements, similarly to BMS. With better flexibility, easier delivery (Figure 7) and the possibility of accessing the side branches, the shape of the modular support of the open-cell type prevailed. Further, the development of a biocompatible polymer coating reduced the inflammatory response and thus the incidence of late thrombosis (4,18,19). With these new generations, DES became the new gold standard between 2018 and 2019 due to statistically significantly better clinical outcomes in the first year after implantation compared to BMS (24). The publication of new ESC/EACTS guidelines (23), which identified DES as the first choice in the treatment of obstructive coronary heart disease in all conditions, also contributed to this improvement.

Despite advances in the development of vascular stents, these still represent a foreign body in the vascular wall and thus promote chronic inflammation, neoatherosclerosis, and therefore restenosis and thrombosis for many years after insertion. Development has been focused on strategies that would leave behind as little foreign material as possible or be as biologically compatible as possible. Polymer-free metalic DESs, polymer DESs that degrade and turn into BMSs after about 6 to 12 months, and stents that attract endothelial progenitor cells with their antibody-coated structure and thus promote faster endothelialisation have been developed (4,5). However, rapid development is now taking place at the top of the "leave-nothing-behind" strategies with

fully degradable DESs (BRSs). Their goal is a relatively short-term support of the vascular wall in a form similar to DES, and with gradual resorption, preservation of endothelium and vasomotor function of the vessel as physiologically as possible. They are made of a framework consisting of one of the polymers (poly-L-lactide, salicylic acid or poly-tyrosine polycarbonate) or a biodegradable metal (magnesium or iron alloy), a drug carrier and an antiproliferative drug. In the development of BRS, the already mentioned paclitaxel is being replaced by newer drugs (sirolimus, everolimus, myolimus and novolimus). Unfortunately, current BRS frameworks are a major drawback of the method and are thus the main reason their use in clinical practice is not recommended (23). Due to their lower strength, the polymers have significantly larger structural elements and up to 240% thicker frameworks compared to DES (Table 1). At the same time, they have poorer resistance to radial forces, a higher incidence of fractures and, due to their larger size, are more difficult to deliver to the target lesion. BRS's current biodegradable metal competitors have a thinner structure at the expense of a stronger framework, which could give them an advantage over polymer BRS in the future (18,19,25). Regardless, currently the most researched and commercially available is the ABSORB polymer bioresorbable vascular stent (Abbott, Illinois, USA) made of poly-L-lactide. These stents were identified by several meta-analyses, the ABSORB II and ABSORB III studies, and the GHOST-EU registry study. Studies have shown currently poorer results in using ABSORB BRS compared to the latest generation of DES (XIENCE, Abbott, DES from cobalt-chromium alloy and with everolimus), but they are expected to beat DES with advances in BRS development, materials and techniques (18,19,26,27).

By developing and reviewing the previously described methods of revascularization, we would like to present the development and significance of progress in the direction of the "leave-nothing-behind" strategies. It is this mindset that is also one of the leading ideas behind the drug-coated balloon technology.

5 Percutaneous transluminal angioplasty using drug-eluting balloons

A DEB consists of a balloon, a drug carrier, and an antiproliferative drug. It first appeared on the market in 2009 to locally apply an antiproliferative drug to the lesion site without a stent, which would remain in the vessel wall and promote inflammation. Because there is no stent, a DEB is smaller and thus more useful in smaller branches of the coronary arteries, in tortuous arteries, bifurcation lesions, and calcifications. Most importantly, there can be no fracture or incorrect placement of the stent (28-31). The balloons used are mostly semi-compliant, and with prolonged inflation (30–60 seconds), the antiproliferative drug is transferred and absorbed upon contact with the vessel wall. The application of the drug itself is thus faster, in higher concentrations than in DES, more uniform over a larger area and is easier to deliver to smaller arteries or arteries that are harder to reach (28). A lipophilic drug must be used for proper absorption, which is difficult when the drug is being transferred during inflation. Due to its hydrophobicity and contact with blood, it could remain stuck to the balloon. The problem was overcome with a drug carrier that allows the transfer of the active ingredient despite its hydrophobicity. The original carrier was iopromide, but later urea, shellac, butyryl-trihexyl citrate (BTH) and a non-polymeric hydrophilic carrier were used. DEBs with a two-layer matrix and without a carrier (DEB Elutax, Aachen Resonance) were also developed. Depending on the carriers (Table 1), the so-called DEB thus have different pharmacokinetics and pharmacodynamics and different recommended balloon inflation times (31,32). The first drug used was paclitaxel, an inhibitor of microtubules and thus an inhibitor of smooth muscle and fibroblast proliferation in the vessel wall, migration of these cells and leukocytes, and extracellular matrix secretion. In most cases, the concentration of the drug on the surface of the balloon is 2–3 μg/mm2, which is then reduced during handling and delivery to the lesion site. In the original carriers (iopromide), according to study data, approximately 20% of the drug was transferred to the vessel wall, 20% of the drug was lost on delivery before expansion, 13% remained bound to the carrier, and approximately 47% was lost in blood circulation upon re-contraction of the balloon and its removal. With newer carriers, the losses are significantly lower. As with stents, the target lesion must be dilated first. This not only increases the diameter of the vessel, but also causes micro-damage to the vessel, which allows better deposition of the drug in the intima and media of the artery (28,30-33).

Numerous studies have been carried out on the attractive method of DEB in order to include it in the treatment of coronary heart disease. DEB could resolve stenosis, reduce inflammatory response and proliferation in the vascular wall and improve late outcome compared to DES due to the absence of foreign material. The most researched DEB area is ISR treatment. Initial studies compared mainly older treatment strategies,

namely POBA for ISR in BMS (32). The superiority of DEB versus POBA in ISR was first demonstrated by the PACCOCATH-ISR study. This demonstrated the advantage of DEB with paclitaxel compared to POBA in BMS ISR (34). The PEPCAD-DES study demonstrated the advantage of DEB with paclitaxel over POBA in different DES ISRs (35). Further studies also confirmed the superiority of DEB against POBA in DES with sirolimus ISR and BMS ISR (35,36). Comparing DEB with paclitaxel to DES with paclitaxel as an ISR resolution method, DEB showed non-inferiority in the following studies: the PEPCAD II study for paclitaxel DES and BMS ISR, the PEPCAD-China study for ISR resolution in different types of DES with mTOR inhibitor drugs, and the ISAR-DESIRE 3 study for ISR in DES with mTOR inhibitors. In the latter, they also demonstrated the superiority of DEB and DES with paclitaxel over POBA (37-39). Studies have led to the inclusion of the DEB and ISR treatment with the IA level of recommendation in the European guidelines for myocardial revascularisation (23).

The use of DEB in *de novo* lesions is less researched. The prospective Valentines II study (40) identified the second-generation of DIOR DEB (Eurocor, Bonn, Germany) with POBA predilatation in 103 patients with stable or unstable angina pectoris and/or documented ischaemia with a *de novo* lesion with stenosis greater than 50%. The study was not limited to anatomically unattractive sites and thus also included lesions in vessels of larger diameter. BMS was used in the study in case of inadequate angiographic results after the use of POBA and DEB. Based on the results of the study, the DEB method was identified as a possible alternative in patients in whom the use of DES was contraindicated (40).

Despite the presented study, the use of DEB in *de novo* lesions is controversial. According to larger meta-analyses and studies, DEB is primarily an attractive alternative to DES for resolving *de novo* lesions that have occurred in arteries with a small diameter (28,29,32). This was first investigated in the PICCOLETO and BELLO studies. The latter included 182 patients older than 18 with stable or unstable angina pectoris or documented silent ischaemia and a maximum of two significant angiographically detected *de novo* lesions, less than 25 mm long, on a vessel less than 2.8 mm in diameter. Patients were randomized to receive IN.PACT Falcon with a paclitaxel-eluting balloon (Medtronic, Inc., Santa Rosa, California) or a Taxus Liberté paclitaxel-eluting stent (Boston Scientific, Boston, Massachusetts). All had previously been dilated with POBA. The study showed that DEB is a good alternative to the use of DES for lesions in coronary arteries less than 2.8 mm in diameter. The late lumen loss was smaller when using DEB (a 0.21 mm difference with 95% confidence interval – 0.34 to – 0.09 mm, $p_{\text{non-inferiority}} < 0.001$, $p_{\text{superiority}} < 0.001$) (41). Otherwise, the PICCOLETO study showed completely different results. In this case, a paclitaxel-eluting DIOR balloon (Eurocor, Bonn, Germany) was used compared to a Taxus Liberté paclitaxel-eluting stent (Boston Scientific, Boston, Massachusetts, USA). The study was completed ahead of schedule due to the apparent superiority of DES (42). In regard to its results, the study is being criticized for predilating the lesions in the DEB group only in 25% and for using DIOR balloons with a known lower target concentration of the drug. These allegations could explain the poorer outcome of the DEB group and the incomparable results with the BELLO study (29).

In 2018, our topic was relaunched by the large prospective, randomized BASKET-SMALL 2 study. It included patients with an indication for PCI (acute coronary syndrome, chronic angina pectoris, silent ischaemia) and an observed lesion in the native coronary artery of 2 to 3 mm in diameter. At predilatation of the lesion, patients were classified into a group with successful predilatation (absence of dissection with TIMI ≤ 2 or more than 30% residual stenosis) and a group with unsuccessful dilatation. The group of 382 patients with successful dilatation of the lesion was then randomized to receive SeQuent Please pablitaxel-eluting DEB (B Braun Melsungen AG, Melsungen, Germany) or Taxus Element paclitaxel-eluting DES (Boston Scientific, Natick, USA). Unfortunately, during the Taxus Element study, stents became unavailable. Thus, they continued with Xience everolimus-eluting DES (Abbott Vascular, Santa Clara, USA). Due to different antiproliferative drugs and thus possible differences in efficacy, they increased the study sample. A total of 376 patients received DES. The study showed noninferiority of DEB by reaching the primary endpoint of the study – significant difference in total MACE after 12 months (95% CI -0.038 to 0.039, p = 0.0217). Although the study lacked strength for the final analysis of the MACE subgroups, the analysis of individual components showed no differences (43).

The largest completed BASKET SMALL 2 study to date was thus the first to demonstrate the non-inferiority of DEB in a larger population than BELLO and compared to the second generation of DES. In doing so, it also confirmed the rationale for further defining the use of DEB.

Table 1: Some vascular stents and drug-eluting balloon catheters with basic characteristics (7,25,30,44,48-50).

Manufacturer	Name	Material	Drug	Diameter of structural elements (μm)
BMS				
Medtronic	BeStent	Stainless Steel		75
Abbott	Multi-Link Vision	Cobalt-chromium		81
First generation DES				
Cordis	Cypher	Stainless Steel	Sirolimus	140
Boston Scientific	Taxus Liberté	Stainless Steel	Paclitaxel	96
Boston Scientific	Taxus element	Platinum-chromium	Paclitaxel	81
Second generation DES				
Medtronic	Endeavor	Cobalt-chromium	Zotarolimus	91
	Resolute	Cobalt-chromium	Zotarolimus with BioLinx polymer	
Abbott	Xience (V, Prime, Xpedition, Alpine, Sierra) family	Cobalt-chromium There is a difference between individual generations in delivery upgrades and increased postdilatation diameters.	Everolimus with fluoropolymer	81
Boston Scientific	Promus Premiere	Platinum-chromium	Everolimus with poly (vinylidene fluoride co-hexafluoropropylene	81
	Promus Element	Platinum-chromium	Everolimus with fluoropolymer	81
DES with biodegradable polymer, first generation				
Biosensors	BioMatrix	Stainless Steel	Biolimus	112
	Axxess	Nitinol	Biolimus	152
DES with biodegradable polymer, second generation				
Boston Scientific	Synergy stent	Platinum-chromium	Everolimus with polylactide glycolic acid	71
Biotronik	Orsiro	Cobalt-chromium	Sirolimus with poly-l-lactic acid	71
BRS				
Abbott	Absorb BVS	Poly-l-lactic acid	Everolimus	150
	The next generation of Absorb stents			120
Elixir	DeSolve	Poly-l-lactic acid	Novolimus	150
	DeSolve, second generation			120
Biotronik	Dreams 2G	Magnesium alloy with polymer support	Sirolimus	150

Manufacturer	Name	Material	Drug	Diameter of structural elements (μm)
DEB				
		Carrier	**Drug**	
Braun	SeQuent please NEO	Iopromide - Paccocath coating with dipping	Paclitaxel 3mcg/mm^2	
Medtronic	In.Pact Falcon/Admiral	Urea – FreePac coating	Paclitaxel 3.5mcg/mm^2	
Aachen Resonance	Elutax	Two-layer drug without carrier	Paclitaxel 2mcg/mm^2	
	Elutax-SV	Three layers of application, an outer layer of dextran and two layers of a drug	Paclitaxel 2.2mcg/mm^2	
Biotronik	Pantera Lux	Butyryl-tri-hexyl citrate (BTHC) - Lux coating	Paclitaxel 3mcg/mm^2	
Eurocor	DIOR I	Crystalline coating, protected by a three-folded balloon	Paclitaxel 3mcg/mm^2	
	DIOR II	Shellac	Paclitaxel 3mcg/mm^2	
Concept Medical	Magic Touch	Phospholipid bilayer (Nanolute technology)	Sirolimus 1.27mcg/mm^2	

In addition to the heterogeneous group of DEBs with paclitaxel described so far (Table 1), a novelty now on the market are DEBs with sirolimus (Magic Touch, Concept Medical Research Private Limited, India). They use a drug with a concentration of 1.27 μg/mm2, which is trapped in the double-layered phospholipid on a hydrophilic basis. This base allows the blood to form a layer under the double-layered phospholipid, which improves the transfer of the drug into the vessel wall. Paclitaxel is mostly absorbed and retained in adventitia, whereas sirolimus shows the same affinity for adventitia and media (30,44). Due to different pharmacodynamics and pharmacokinetics, Magic Touch could represent a major step forward in the development of DEB. It was evaluated by an openly prospective, multicentre Nanoluté study (44). A total of 332 patients with 356 lesions were included in the Magic Touch DEB treatment (Concept Medical Research Private Limited, India). Patients enrolled in the study were over 18 years old and had stable angina pectoris, silent ischaemia, acute coronary syndrome, ISR, small-diameter coronary artery disease (vessel diameter in the study was 1.5 to 4.00 mm), bifurcation lesions, or multivascular disease, and there were also patients treated with hybrid strategies. According to the published results, the possibility and safety of using DEB with sirolimus in different types of lesions was shown (44).

One of the future major open prospective studies that could provide even more information on the use of Magic Touch DEB is the EASTBOURNE study. It includes all coronary heart disease patients with clinical indications for PCI. It will primarily assess the need for target lesion revascularization (TLR) 12 months after the procedure, and secondarily, the angiographically assessed success rate of revascularization and MACE (major adverse cardiovascular events) at 6, 12 and 24 months (44).

Given the rapid development of intervention methods so far, we can also expect continuous improvements in materials and pharmacological agents in the field of DEB. DEBs with newer antiproliferative drugs from the mTOR inhibitor family and with better pharmacological and pharmacodynamic properties will be used. At the same time, newer nanocarriers will be developed to ensure maintenance of the drug concentration on the balloon during transfer, homogeneous application of the drug to the lesion site in targeted concentration and targeted and long-term therapeutic concentration of the drug in deeper layers, i.e. in arterial adventitia (30). We can also expect the identification of DEB in combination with "scoring and cutting" balloons, which could improve drug deposition with controlled microdissections and in combination with bioresorbable stents (28). It is also possible in the future to give priority to the use of DEB when there is a high risk of bleeding with DAPT therapy. Since there is no stent and thus less thrombogenicity,

a shorter-term dual antiaggregation therapy (DAPT) is possible with DEB. Initially, a four-week therapy was defined by a number of smaller randomized studies and opinions of national associations (45). However, a more extensive meta-analysis by Kleber et al. (46) confirmed the sufficiency of only one month's DAPT with the use of DEB for stable coronary heart disease and *de novo* lesions. However, a recently published retrospective study demonstrated the safety of a one-month DAPT therapy even with the use of DEB for stable coronary heart disease, regardless of the type of lesion (45).

Further studies will try to define more precisely the characteristics of patients that would predict a better end result when using DEB. According to the results so far, these are most likely to be patients with anatomically unfavourable lesions and lesions in smaller coronary arteries. The need for stents and their development will remain, if nothing else, because of their need in the event of hemodynamically important dissections and acute vascular occlusions seen in the past in POBA. However, with favourable study results, an approach with lesion predilatation could be established and then, with favourable hemodynamic results, the application of DEB instead of DES. The latter would be reserved for suboptimally resolved lesions (28,29,32).

6 Conclusion

Based on current methods, ESC/EACTS guidelines were developed in 2018 (23) recommending the use of DES in the treatment of obstructive coronary heart disease, regardless of the clinical presentation of issues, lesion type, planned noncardiac surgical procedure, anticipated duration of treatment with dual antiaggregation therapy and concomitant anticoagulant therapy (level I recommendation, level A evidence). DEB, on the other hand, is an equivalent alternative to DES in the treatment of ISR with BMS and DES (level I recommendation, level A evidence). At present, the use of DEB is not recommended unless it is an ISR treatment (23). Also, the current 2017 ESC guidelines for antiaggregation therapy (47) recommend six months of treatment with DAPT using DEB in stable coronary heart disease based on studies of the use of DEB in ISR (PEPCAD China ISR, ISAR DESIRE 3, RIBS IV). According to the larger volume of better research results mentioned above, we can expect a change in the recommendations in the future.

The future is bringing both the development of DES and DEB in the direction of the "leave-nothing-behind" strategies. The DEB group is extremely heterogeneous with different drugs and carriers, which partly explains the conflicting results of some studies.

However, with the recent rapid development of DEB and the use of newer technologies, we need more qualitative data from larger randomized studies that will compare the use of DEB and DES in different types of lesions to more accurately define the site of use of newer DEBs.

Conflict of interest

None declared.

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