Drug-coated balloons for the management of coronary artery disease

Drug-coated balloon (DCB) angioplasty enables coronary intervention without permanent metallic implants and may be particularly beneficial in patients with high clinical or anatomical risk. While evidence in de novo lesions remains inconsistent, ongoing trials such as BASKET-BALL aim to clarify its role versus DES. In the future, DCB and stents may be used complementarily to reduce permanent stent burden and improve outcomes.

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The history of interventional cardiology began almost 50 years ago in Switzerland with the inflation of a balloon. On September 17, 1977, the first percutaneous transluminal coronary angioplasty was performed in the catheterization laboratories of the Cantonal Hospital Zurich, when for the first time Andreas Grüntzig treated a patient successfully with a plain old balloon angioplasty (POBA) in a coronary artery (1). Although this achievement was historical, initial results were flawed by early complications such as flow-limiting dissections in up to 10% and both restenosis and elastic recoil in up to 50% of cases, necessitating in-house surgical backup with the option for emergency coronary artery bypass surgery.

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To overcome these limitations, so-called stents were developed, i.e., intraluminal scaffolds formed from narrow metal struts keeping the vessel open. While the first stents led to a good and reproducible short-term result, the use of these bare-metal stents led to high rates of in-stent restenosis due to a late vascular response with inflammation and neointimal hyperplasia due to smooth muscle cell proliferation. To inhibit neointimal hyperplasia, cytostatic agents such as paclitaxel and sirolimus embedded in a polymer were added to the stent surface, forming the drug-eluting stents (DES). The inhibition of neointimal hyperplasia had an impressive effect on in-stent-restenosis rates, wherein sirolimus showed superior results than paclitaxel on late lumen loss. While the first generation of DES showed a good efficacy with low rates of instent-restenosis, there were increased rates of late stent thrombosis with high mortality and morbidity rates. However, second- and newer-generation stents with improved design and also improvements in implantation techniques led to a decrease in the frequency of this feared and dramatic complication. Currently, the latest-generation DES are the mainstay of interventional treatment of coronary artery disease with reproducible results.

So, all good with DES? Not quite. Data from large registries show a steady increase in stent-associated complications after the initial 12 months of appr. 2 to 3% per year, irrespective of the type of device used (2). These complications encompass entities such as instent-restenosis but also late or very late stent thrombosis, which are associated with considerable morbidity and mortality. In addition, stents require a certain duration of dual antiplatelet therapy after implantation, which may be associated with relevant bleeding complications. Therefore, the use of a metallic implant to treat coronary artery disease is not as harmless as it is often said but confers a certain potential of both ischemic and bleeding complications. In addition, there are certain patient groups with increased rates of complications after stent implantation, mainly those with a higher probability of stent failure due to high clinical or anatomical risk. In this context, high clinical risk includes diabetes mellitus, chronic kidney disease, acute coronary syndromes, high bleeding risk, and the elderly, whereas high anatomical risk includes small vessel disease, bifurcation lesions, long lesions, and lesions in multiple vessels. In these situations, a novel treatment approach without metallic implants could be helpful to decrease event rates.

Drug-coated balloons (DCB) consist of semi-compliant balloons that are coated with drugs that inhibit neointimal growth, such as paclitaxel and sirolimus and its derivatives (3) *(Fig. 1)*. There are different technical possibilities to ensure a safe fixation of the antiproliferative agent on the balloon surface and its transfer into the vessel wall; in most cases, the drug is embedded in a matrix or in microspheres. There are many different designs and compositions of DCB; therefore, no class effect can be assumed, and every device has to prove its own efficacy and safety. While the classical DCBs are coated with paclitaxel, newer designs use sirolimus, which is less lipophilic but has a higher antiproliferative efficacy. It can be clearly noted that – despite continuous rumors, which are clearly wrong - there is no increased mor-

tality with the use of paclitaxel in coronary artery disease as proven by a large meta-analysis of randomized controlled trials using paclitaxel-coated balloons (4).

As described in current guidelines (5) *(Fig. 2)*, a prerequisite of proper DCB use is an optimal lesion preparation, which may include the use of specialist balloons or tools for calcium modification. The use of DCB is recommended only if after lesion preparation neither a residual stenosis of more than 30% nor a flow-limiting dissection is detected. However, repeated and prolonged balloon inflations or tools such as cutting or scoring balloons, high-pressure non-compliant balloons, lithotripsy, and rotablation or rotational atherectomy usually allow for acceptable angiographic results.

The first clinical use of DCB was reported in patients with in-stent-restenosis by Scheller et al 20 years ago (6). Since then, in-stent-restenosis developed to the classical indication for DCB, although recent guidelines downgraded it in favor of DES (7). However, this downgrade was due to an inadequate interpretation of a large meta-analysis of all available randomized studies in the field, among them early studies where neither intravascular imaging nor a proper lesion preparation before DCB use was done, making DES slightly more effective than DCB at the cost of a worse safety profile (8). Anyhow, the implantation of a second stent layer in an already delicate environment with stent failure definitely makes no sense and should be avoided.

Since then, other indications for the use of DCB have been evaluated in de-novo disease, specifically in anatomical situations where stents tend to fail *(Fig. 3)*. The most prominent of these indications is the use of DCB in small vessel

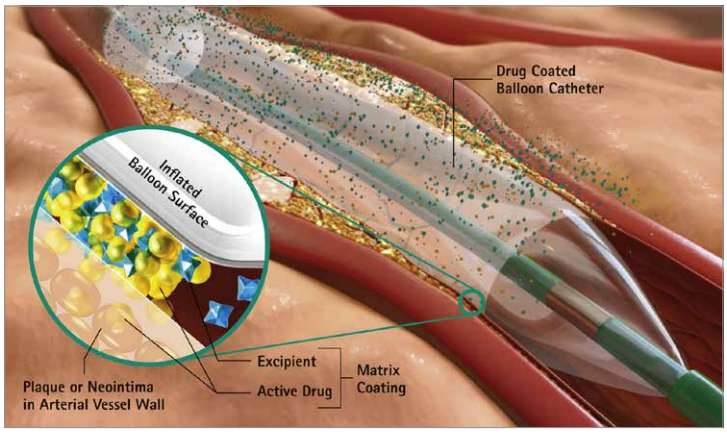

Fig. 1: Drug-Coated Balloon Technique and Mechanism of Action (Reproduced with permission from [5])

disease, where clinical data is quite robust. The BASKET-SMALL 2 trial was the first large trial in the field and tested DCB against second-generation DES in coronary artery disease <3 mm in diameter and found similar event rates for both groups, establishing non-inferiority of DCB against DES at 1 year (9). In a recent meta-analysis of randomized controlled trials in small vessel disease, even superiority of DCB against DES could be established for a combined endpoint, i.e., all-cause mortality, myocardial infarction, target lesion thrombosis, or target vessel revascularization, at 3 years (10). Another frequent indication is bifurcation lesions, where DCB can be used for both the main and side branch or the side branch only (11). While the use of DCB in the side branch has been proven beneficial against POBA, a

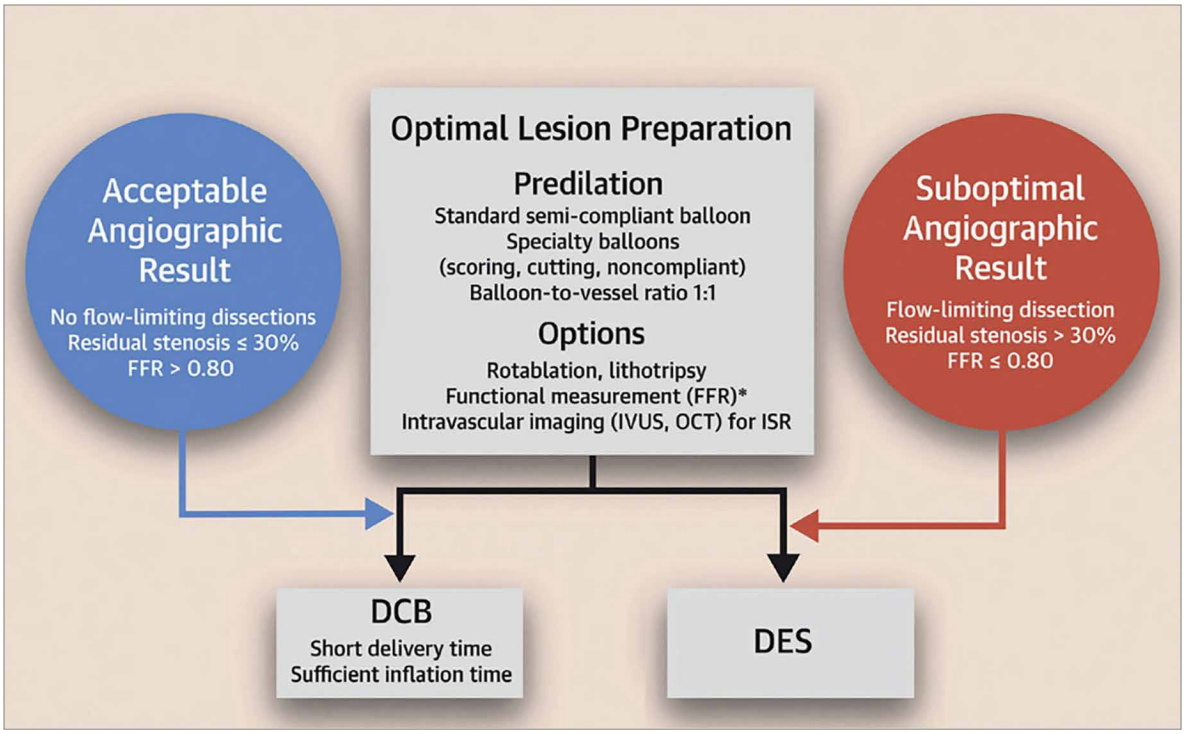

Fig. 2: DCB-Only Strategy for PCI in Coronary Artery Disease (Reproduced with permission from [5])

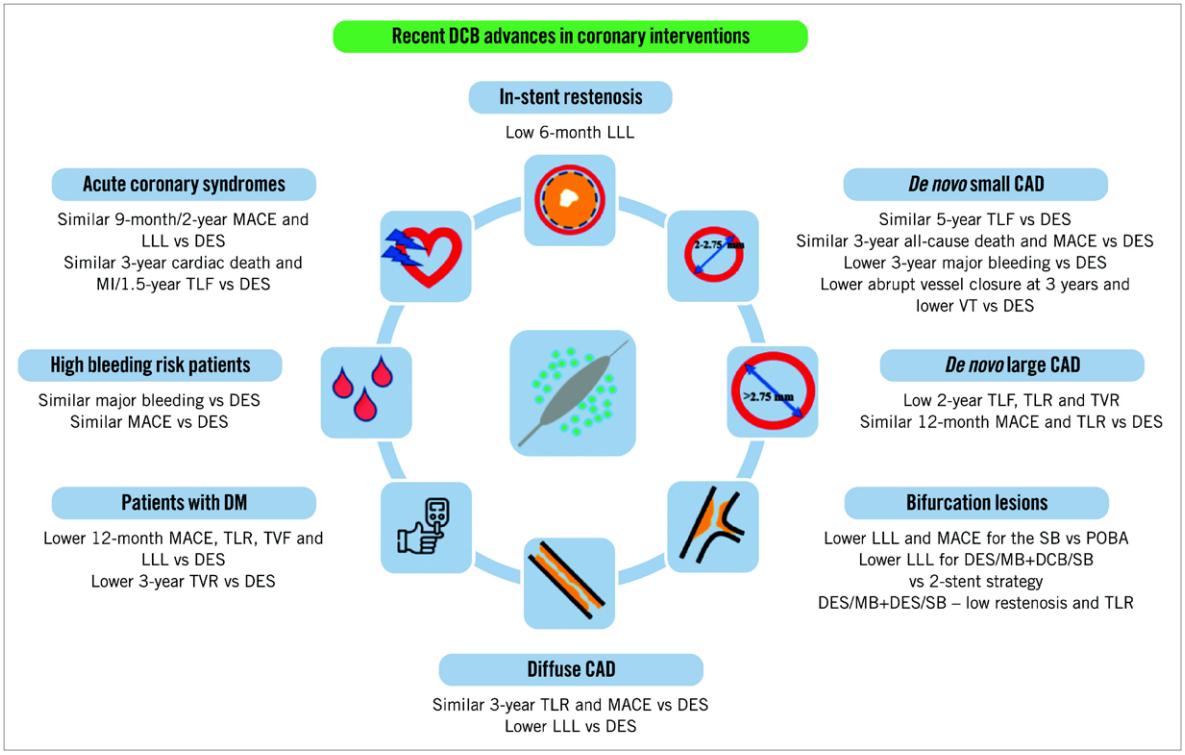

Fig. 3: Potential indications of drug-coated balloons in coronary interventions (Reproduced with permission from [19]).

pure DCB-only approach is currently being tested in ongoing studies. Other indications are based on less evidence but show good clinical results, e.g., long diffuse lesions and multivessel disease.

While certain anatomic situations with high-risk coronary lesions are suitable for DCB treatment, there are some clinical situations where DCB may be beneficial as well, e.g., in diabetic patients, patients with acute coronary syndromes, and patients with high bleeding risk. In a prespecified subgroup analysis of diabetic patients from BASKET-SMALL 2, the need for target vessel revascularization was significantly lower with DCB versus DES (12). In patients with non-ST-elevation myocardial infarctions, treatment of coronary de-novo lesions with DCB was non-inferior to stenting with bare-metal stents or DES (13), while in patients with ST-elevation myocardial infarction, a DCB strategy was noninferior to DES in terms of fractional flow reserve assessed at 9 months (14). In patients with high bleeding risk, percutaneous coronary intervention with DCB was superior to bare-metal stents, since DCB requires a considerably shorter duration of dual antiplatelet therapy than DES (15).

While available evidence in single important high-risk populations demonstrates a potential benefit of DCB, the creation of evidence in all-comer patients will be the next step to make the technique more popular. Recently, two large, randomized trials in all-comer de-novo disease were presented. The REC-CAGEFREE I trial investigated the use of a paclitaxel-coated balloon against a sirolimus-eluting stent in de-novo non-complex coronary artery disease (16). At 2 years, DCB did not reach non-inferiority against DES regarding a combined clinical endpoint of cardiovascular death, target vessel myocardial infarction, and clinically and physiologically indicated target lesion revascularization. In contrast, the SELUTION De Novo trial showed non-inferiority for a sirolimus-coated balloon against DES regarding a clinical endpoint of cardiac death, target-vessel myocardial infarction, and clinically driven target vessel revascularization after 1 year in an all-comer population (17). Reasons for the conflicting results in the two trials may lie in the different performance of the DCB used since there is no class effect for DCB, the varying experience of the investigators as measured by the stent bailout rates, and the selection of patients, i.e., non-complex disease vs. all-comers. SELUTION De Novo was a strategy trial enrolling all-comer patients and allowed randomization before lesion preparation with a respective low stent rate of 21%, whereas REC-CAGEFREE I enrolled patients with low-risk lesions after lesion preparation only and despite this had a respective high bailout stent rate of 9%. Of note, SELUTION De Novo showed a specific benefit of the DCB strategy in certain high-risk patient subgroups such as the elderly and patients with high bleeding risk, long lesions, multivessel disease, and calcifications.

Therefore, results in de-novo lesions are inconsistent, which makes another large trial addressing potential pitfalls necessary. The BASKET-BALL randomized controlled trial (NCT07363161) started enrollment in Switzerland and other European countries and will address most of these issues: it will be a strategy trial using a DCB with proven efficacy, enroll patients only in experienced centers, and will examine a patient population where the benefit of DCB against

DES might be the highest, i.e. patients with a high clinical or anatomical risk such as diabetes mellitus, chronic kidney disease, acute coronary syndromes, high bleeding risk, the elderly, bifurcation lesions, long lesions, and lesions in multiple vessels.

While we await more data, what will be the future? DCB and DES are rather complementary but not exclusive treatment options that may be combined in a hybrid approach - observational data show decreased event rates when the number of metallic implants is reduced (18). Therefore, the reduction of stent burden in high-risk anatomical or clinical situations may already help to overcome the restrictions of current stent therapy and allow for improved results. Specifically, the use of more DCB instead of DES could lead to interventional results that might compete with the results of coronary artery bypass graft surgery in multivessel disease. In addition, the combination of DCB with bioresorbable scaffolds instead of permanent metallic implants may be a perfect match to leave nothing behind in the interventional treatment of coronary artery disease, but the performance of these devices must be proven in large, randomized trials before wider clinical application. Therefore, the quest for continuous improvement of the interventional treatment of coronary artery disease continues... □

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