

BACK TO THE FUTURE: DCB USE INSTEAD OF DES FOR THE TREATMENT OF COMPLEX, NATIVE CORONARY ARTERY DISEASE

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Abstract

The increasing complexity of coronary artery lesions in patients with significant co-morbidities and the need for revascularization, but with the ineligibility for surgical approach, has turned the percutaneous coronary intervention a challenging task, especially in a setting in which short and long term complications after drug-eluting stent implantation are high. Drug Coated Balloons (DCB) have become an important tool to replace stent placement in specific situations such as small coronary artery disease and in-stent restenosis. Although preliminary data of DCB use in complex lesions is promising, the available data is still limited. Therefore, in this article we review the most recent and relevant literature about the use of DCB in native vessel disease and in complex anatomies/patients, and pretend to justify the necessity to develop well design trials about the use of this therapy in such settings, also thinking at DCBs as a complementary tool to drug-eluting stents.

Introduction

In the past few years there has been an increase in the clinical and anatomical complexity of Coronary Artery Disease (CAD) ¹. A large amount of patients that present with moderate to high risk anatomical classification (SYNTAX) but associate also high peri-procedural mortality risk measure by EuroSCORE II and STS score, have been classified as ineligible for coronary artery bypass grafting surgery, causing a growing number of patients requiring complex Percutaneous Coronary Interventions (PCI). Unfortunately, such patients which are treated daily in our catheterization laboratories were not previously included in adequately powered randomized clinical trials ²⁻⁵.

In 2016 Kirtane et al. categorized patients with severe CAD needing revascularization but with significant medical co-morbidities, now called “Complex Higher-risk and Indicated Patients” (CHIP). Those patients are characterized by features of 3 clinical aspects: 1) patient risk factors and co-morbid conditions (including those that preclude surgical or percutaneous revascularization); 2) location and complexity of coronary anatomy; 3) hemodynamics, ventricular function, and concomitant valvular heart disease ⁶.

Another piece of the story is the necessity to achieve a complete or near complete revascularization in order to improve the clinical outcome of our patients. In the particular case of CHIPS, the attempt to reach these goal carries a high amount of metal implantation (Drug-Eluting Stents-DES) ⁷. Conversely, Drug Coated Balloons (DCB) are an emerging technology which nowadays in 2021 should aim at significantly decrease the use of stents in such complex scenarios, thanks to the fact that they have demonstrated to be easy to use, safe and with good clinical outcome in some groups of patients with CAD ^{8,9}.

Stent overview

Despite the continuously improved and new advances in the design of new generation DES with thinner struts and biodegradable-polymer, this technology still presents several limitations such as inadequate expansion, expansive remodeling, abnormal vasomotion and the occurrence of neoatherosclerosis, In-Stent Restenosis (ISR) and stent thrombosis ^{10,11}. In simple lesion characteristic models this new generation DES has shown to have a permanent risk of Target Lesion Failure (TLF) ranging between 0.8-1% yearly ¹². Despite such devices were not assessed in more complex lesion settings (chronic total occlusions, complex bifurcations, very long lesions, highly calcific lesions), we can argue that the outcome would be even worse in such cases. In case of small vessels, for example, the same device is associated with double risk of TLF ¹³.

If we put also the high risk, CHIP patient into this context, we can easily expect even higher rates of stent failures, considering the higher risk of stent malapposition, underexpansion, delayed reendothelialization and the need for shorter Dual AntiPlatelet Treatment (DAPT) due to higher hemorrhagic risk.

There are a number of well-established factors associated with the risk of thrombotic complications after stent-PCI, which can be divided into clinical, procedural and technical characteristics (tab. I). A value of stented length over 31.5 mm has been found a threshold for the prediction of stent thrombosis ^{14,15}.

Drug Coated Balloon overview

Technical aspects

The use of DCB to treat CAD lesions is based on its ability to transfer an antiproliferative drug into the vessel wall during balloon inflation without the use of metal permanent implants. The first drug studied was paclitaxel with sirolimus adopted more recently. In order to have the drug persisting in the vessel wall, a carrier is usually adopted ^{16,17}.

Adequate lesion preparation in most cases is needed before planning to

Table 1 - Risk factors associated with PCI with stenting complications-the CHIP patient.

<i>Clinical</i>	<i>Procedural</i>	<i>Technical</i>
History of MI	Multi-vessel CAD	Multiple stents
Previous PCI	Coronary chronic total occlusion	Number of stents per lesion
Poly-vascular disease	STEMI / NSTEMI	Number of vessels treated
Diabetes Mellitus	Early discontinuation of antiplatelet	No post-dilation ballooning
Chronic kidney disease	Previous CABG	Smaller stent diameter
HF with reduce EF		Residual dissection
History of bleeding		
Malignancies		
History of ischemic stroke		
Recent major surgery		

Legend: PCI: Percutaneous Coronary Intervention; CHIP: Complex Higher-Risk and Indicated Patient; MI: Myocardial Infarction; HF: Heart Failure; EF: Ejection Fraction; CAD: Coronary Artery Disease; STEMI: ST-Elevation Myocardial Infarction; NSTEMI: Non ST-Elevation Myocardial Infarction; CABG: Coronary Artery By-pass Grafting.

perform any coronary angioplasty either with stent or DCB. Lesion preparation mainly facilitates delivery of the stent or the DCB and decreases the risk of damage. Secondly, it helps to determine the optimal or real size and length of the lesion. And finally, it improves the chance to have good outcomes after DCB delivery¹⁸. Aggressive lesion preparation can be achieved with semi-compliant balloons 1:1 to the distal reference diameter, but one can start with smaller balloons in cases of tortuous or highly calcific lesions. Then, it is usually suggested to escalate to high-pressure noncompliant or plaque modification (cutting, scoring) balloons in case of sub-optimal results. In heavy calcified lesions rotational atherectomy, lithotripsy, or prolonged balloon dilation, may be required¹⁶. Before DCB delivery, it is usually advisable to reach less than 30% of residual stenosis with TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 and non flow-limiting dissections¹⁹.

Clinical outcomes

DCB were initially used for the management of ISR of Bare Metal Stents (BMS) and later DES with robust clinical results. Therefore, since 2014 the ESC/EACTS Guidelines elevated DCB to DES use in this setting with recommendation Class I and Evidence type A²⁰.

In the more recent years, the use of DCB increased and such devices were used in the native vessel disease setting, including small coronary artery disease, with strong evidence of support derived by studies such as BELLO, BASKET-SMALL 2, RESTORE SVD and PICCOLETO 2²¹⁻²⁴. BELLO trial (2012) included 182 patients with lesions <2.8 mm of diameter and demonstrated an improved angiographic outcome with In.Pact paclitaxel coated balloon, along with reduced MACE rates at 3 years as compared to first generation (Taxus) DES²¹. Later BASKET-SMALL 2 trial had 758 patients randomized between DES and Sequent Please paclitaxel coated balloon, showing the

non-inferiority of DCB in terms of MACE at 12 and 36 months²². More recently, in PICCOLETO 2 trial we compared Xience DES and Elutax SV, demonstrating superior late lumen loss with the latter (0.04 vs 0.17 mm, $p=0.001$) and no difference in MACE at 12 months (5.6% vs 7.5%, $p=0.55$)⁹.

Recently, the complex setting of ST-elevation myocardial infarction has been studied in the REVELATION trial which randomly assigned patients to DCB or DES after pre-dilatation. The mean flow fractional reserve assessed during angiographic follow up at 9 months was 0.92 ± 0.05 in the DCB group ($n=35$) and 0.91 ± 0.06 in the DES group ($n=38$), without statistically significant difference ($p=0.27$)²⁴.

Large vessels

Until recently, treating coronary artery stenosis in vessels >3 mm of diameter was anecdotal and feared by the interventional cardiologist due to the theoretical larger infarction following potential acute vessel closure. However, in the smaller vessel setting this complication has not been shown and all DCB tested have always been considered a safe treatment option.

More recently, a growing evidence as a support for the use of DCB in larger coronary arteries showed this strategy to be safe and efficient, at least in some clinical settings.

The FALCON registry enrolled 757 all-comer patients treated with the In.Pact technology, showing a good safety and efficacy profile at 1 year²⁵.

Later, the randomized DEBUT study performed in Finland enrolled 220 patients with lesions on coronary arteries up to 4.0 mm in patients at high risk of bleeding. Authors found DCB group to be non-inferior to BMS in terms of MACE at 9 months. Again, no acute vessel closure was described in the DCB arm, but 2 stent thromboses were described in the BMS cohort²⁶.

The growing complexity of coronary artery lesions treated daily in our catheterization laboratories (fig. 1) is well represented in the international, multicenter, investigator-driven prospective EASTBOURNE registry, the largest study on DCB so far. EASTBOURNE enrolled 2.123 patients treated with the first sirolimus-coated balloon marketed in Europe, Magic Touch. TLR was the primary endpoint and follow up is still ongoing. During EuroPCR 2021 the basal clinical characteristics of this registry have been presented (Presenter: B. Cortese). The patients included shared a wide variety of clinical presentations, such as non ST-elevation MI (21%), unstable angina (17%) and ST-elevation MI (8%). One of the most important characteristics about this registry is the high amount of patients with diabetes mellitus (40%) and multi-vessel coronary disease (56%). Differently from other similar registries, in EASTBOURNE the type of coronary lesions for the first time showed more de novo instead of ISR lesions (54%), whereas in 84% of the ISR cases this stent complication occurred in previously implanted DES. Lesion preparation, which as we depicted earlier is of paramount importance before DCB use, was performed in 93% of the cases. Interesting, in only 7.3% of the cases a stent was implanted in bailout fashion, due to flow-limiting dissection. We recently published the interim analysis of this study, which showed a good safety and efficacy profile at 12 months²⁷.

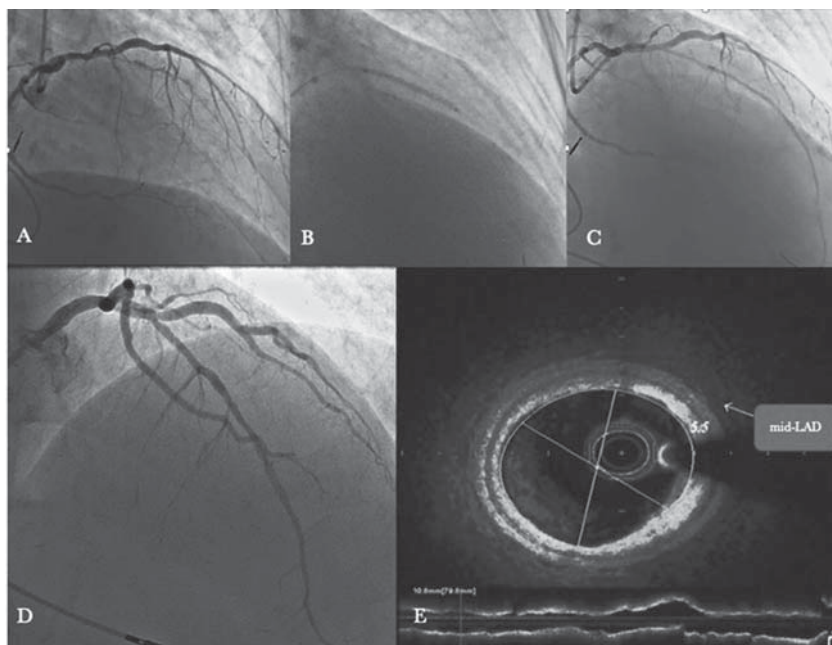


Fig. 1. Chronic total occlusion treated with DCB. A: basal angiography showing the occlusion of mid-left anterior descending artery; B: long paclitaxel-coated balloon use; C: final angiographic result; D: 6-month angiographic result, showing lumen dimensions increase; E: 6-month optical-coherence tomography assessment showing total vessel healing and increased dimensions of the lumen.

DCB in native vessel disease-the future

Which is the future of DCB in native vessel disease? We believe that the role of DCB, either eluting paclitaxel or sirolimus, will be more important in the next decade. We are currently seeking more clinical data to create a more solid scientific background in this setting. TRANSFORM II trial (ClinicalTrials.gov Identifier: NCT04893291) is an international randomized controlled trial which is enrolling patients with native vessel disease between 2.0-30 mm of diameter, and will compare SCB to current generation DES. Primary endpoint is TLF at 1 year where the non-inferiority vs. SCB is hypothesized.

The role of DCB in the complex lesion setting (very long lesions, chronic total occlusions) will be assessed in the PICCOLETO III trial, an international randomized clinical trial which will compare DES to paclitaxel or sirolimus DCB and will follow up the patients up to 5 years: will the superiority of DCBs demonstrated on the long term?

And then? We are still convinced that the role of DES will play a pivotal role in future interventional cardiology, but we would like to stress on the concept that the amount of metal implanted in complex lesions should be restricted, therefore a “hybrid therapy” with limitation of total DES use (spot stenting) on a backbone of drug eluted by means of DCB will be the way to go in our current and future, complex patients (fig. 2).

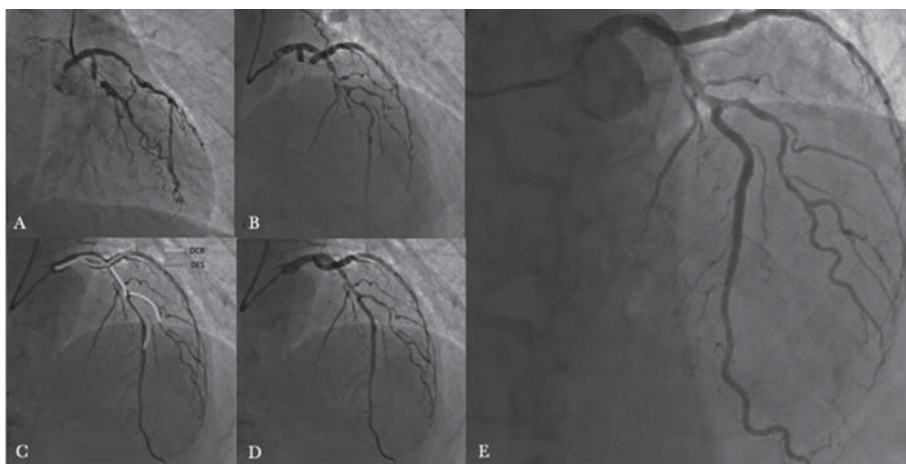


Fig. 2. A, B: left coronary artery with highly complex lesions. C: planning of the procedure with DES and DCB, used to spare the trifurcation; D: final angiographic result; E: 3-month angiographic result.

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