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Drug-coated balloon combined with drug-eluting stent for the treatment of coronary bifurcation lesions: insights from the HYPER study

Dario Pellegrini[1], Michael Donahue[2], Damiano Regazzoli[3], Delio Tedeschi[4], Marco Loffi[5], Mariano Pellicano[1], Giuseppe De Blasio[1], Maurizio Tespili[1], Giulio Guagliumi[1], and Alfonso Ielasi[1]*

[1]Cardiology Division, IRCCS Ospedale Galeazzi Sant'Ambrogio, Via Cristina Belgioioso 173, 20157 Milan, Italy; [2]Department of Cardiology, Policlinico Casilino, via Casilina 1049, 00169 Rome, Italy; [3]Invasive Cardiology Unit, Humanitas Clinical and Research Center, IRCCS, via Alessandro Manzoni 56, 20089 Rozzano, Italy; [4]Interventional Cardiology, Istituto Clinico Sant'Anna, Via del Franzone, 31, 25127 Brescia, Italy; and [5]Unità Operativa di Cardiologia, Azienda Socio Sanitaria Territoriale di Cremona, Viale Concordia, 1 26100 Cremona, Italy

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True coronary bifurcation lesions (CBL) represent a challenging scenario for percutaneous coronary interventions (PCI), and are associated with a higher risk of target lesion failure (TLF), particularly when two stents are implanted. A hybrid strategy combining a drug-eluting stent (DES) in the main branch, and a drug-coated balloon in the side branch may improve outcomes by reducing the total stent length while maintaining an effective anti-prolipherative action. In this sub-study of the HYPER trial, 50 patients with true CBL were treated with a hybrid strategy: procedural success was 96%, one case of peri-procedural myocardial infarction and one case of TLF (in a DES-treated segment) at 1 year were reported. This study suggests that such a hybrid strategy may be a safe and effective option for true CBL PCI, and warrants additional investigations to compare outcomes with standard of care strategies.

Introduction

Despite technical and technological advancements, true coronary bifurcation lesions (CBL) remain one of the most complex yet common scenarios in percutaneous coronary interventions (PCI), accounting for up to 20% of the procedures.[1,2] Compared to standard non-bifurcation lesions, major issues persist, like technical complexity and the increased rate of adverse events,[3,4] especially in terms of target lesion failure (TLF). This is mainly due to the extension of atherosclerosis, which is often underestimated by angiography, and the three-dimensional interaction between the anatomy of the bifurcation and the deployed stents.

The ostium of the side branch (SB) seems to be particularly prone to restenosis due to smaller diameter and abnormalities in shear stress, and this is worsened in case of the presence of multiple layers of stent struts, a well-known predictor of TLF at follow-up.[3,4] Thus, the current consensus documents[5] recommend, whenever possible, a provisional strategy based on the implantation of a single stent on the main branch (MB), with the addition of a second stent on the SB only if strictly needed. Even in case of a single stent, provisional strategy considers an optimization of the SB, but this is performed through plain old balloon angioplasty (POBA), which does not tackle intimal hyperplasia and restenosis.

Drug-coated balloons (DCB) have proved to be a viable alternative to standard drug-eluting stents (DES), being non-inferior to DES in small vessels and in-stent restenosis, thanks to their ability to target restenosis

*Corresponding author. Tel: +390283506765, Email: alielasi@hotmail.com

while avoiding the implantation of permanent metallic struts.

The application of a 'hybrid strategy' through the association of DCB and DES, may provide interesting advantages in CBL PCI, by limiting the number of implanted stent while maintaining a sustained anti-proliferative effect.[6]

This substudy of the HYPER (*A HYbrid APproach Evaluating A DRug-Coated Balloon in Combination With A New Generation Drug-Eluting Stent in the Treatment of De Novo Diffuse Coronary Artery Disease*) trial[7] aimed at assessing the clinical outcomes of such a hybrid strategy for the treatment of true CBL.

Methods

This is a substudy of the HYPER trial (NCT03939468), a prospective, single-arm, multicentre, pilot study aimed to assess the feasibility, safety, and efficacy of a hybrid approach combining a DCB and new generation DES for the treatment of *de novo* diffuse coronary artery disease, defined either as lesions longer than 28 mm or CBL, with the involvement of a segment with a reference vessel diameter (RVD) < 2.75 mm. Details about study design and methods have been previously described,[7] and 1 year results of the overall population have been recently released. The current paper is a sub-analysis of the bifurcation group.

Briefly, the study enrolled patients with chronic or acute coronary syndromes and a CBL involving the SB and at least one of the main vessel (MV) or the MB, i.e. 1.0.1, 0.1.1 or 1.1.1 lesions according to the Medina classification.[8] The 'hybrid strategy' consisted in the implantation of a new generation DES in the MV-MB axis, and DCB inflation for the treatment of the SB lesion. Per protocol, the RVD of the DES-target segment (MV-MB) should be ≥2.75 mm, while RVD of the DCB-target segment (SB) should be ≥2.0 mm to <2.75 mm, according to visual estimation. The new generation DES-type implanted was left at operator discretion, while the DCB used was the Restore (Cardionovum GmbH, Germany), a paclitaxel-eluting balloon with a drug concentration of 3.0 mg/mm^2. Pre-dilatation was mandatory before DCB inflation, according to the current international recommendations (balloon-to-vessel ratio 0.8-1.0, semi-compliant or non-compliant balloon according to local practice).[9] Drug-coated balloon could be inflated either before or after DES implantation, with or without final kissing balloon, according to clinical judgement. In case of good angiographic result after pre-dilatation, defined as residual diameter stenosis (DS) ≤ 30%, TIMI 3 flow and no dissection or type A-B dissection,[10,11] the procedure ended with at least 30 s (optimally 60 s) DCB inflation. Otherwise, the result was defined as a procedural failure and warranted the implantation of a second DES in SB. Post-procedural dual antiplatelet regimen was prescribed according to the international guidelines.[12]

Angiographic data were reviewed by an independent core lab located in the *University of Ferrara* for quantitative coronary angiography (QCA—Medis Suite Solutions, Leiden, the Netherlands) analysis.

Clinical follow-up was performed at 30 days, 6 months and 1 year by in-hospital visit and/or telephone contact.

Endpoint definitions

The primary endpoint was defined as a device-oriented composite endpoint (DOCE) of cardiac death, target vessel myocardial infarction (TV-MI) and ischemia-driven TLR (ID-TLR) in the DES- and/or the DCB-treated segment within 1 year after the index procedure. Peri-procedural MIs were not included in the primary endpoint as per definition.

Secondary endpoints are the following:

- Procedural success, defined as both DES/DCB delivery and implantation at the 'target' lesion site with <30% DS in the DCB-treated segment and <10% DS in the DES-treated segment and distal TIMI 3 flow.
- Peri-procedural MI, defined as an elevation of cardiac biomarkers (troponin or creatine kinase-myocardial band) >5 times the upper normal limit in addition with suggestive symptoms and/or new ischemic changes.
- Individual components of the primary composite outcome (cardiac death, any TV-MI excluding peri-procedural MI, ID-TLR) at 1-year follow-up.
- Any definite/probable DES- or DCB-treated segment thrombosis or occlusion at 1-year follow-up.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range, and were compared with Student's *t* test or Mann-Whitney *U* test according to their continuous or non-continuous distribution. Categorical variables are presented as counts and percentages and were compared with χ^2 or Fisher's exact tests. A *P* value < 0.05 was deemed as statistical significant. Time-dependent analyses were performed with the Kaplan-Meier estimate method.

Results

Fifty patients with true CBL were enrolled in the HYPER study.

Mean age was 67.9 ± 10.3 years, and 80% of the patients were male (*Table 1*). Eighteen patients (36%) had a history of diabetes mellitus, and 48% were affected by multivessel coronary artery disease. Twenty-six percent of the patients had a history of previous MI, while one-third of them had a history of prior myocardial revascularization (36% and 8% reporting previous PCI and CABG, respectively).

Per protocol, all lesions involved the SB and 76% of them involved both the MV and the MB (Medina 1.1.1). Half of

Table 1 Baseline characteristics of the study population

	Patients (*n* = 50)
Age, (years), mean ± SD	67.9 ± 10.3
Male, *n* (%)	40 (80.0)
Diabetes mellitus, *n* (%)	18 (36.0)
Insulin-dependent diabetes mellitus, *n* (%)	10/18 (55.5)
LV ejection fraction, % ± SD	51.8 ± 7.2
Acute coronary syndrome at admission, *n* (%)	4 (8)
Multivessel coronary artery disease, *n* (%)	24 (48)
Previous myocardial infarction, *n* (%)	13 (26)
Previous PCI, *n* (%)	18 (36)
Previous CABG, *n* (%)	4 (8)
Chronic kidney disease (eGFR <60 mL/min), *n* (%)	0
Peripheral artery disease, *n* (%)	2 (4)
Prior stroke, *n* (%)	1 (2)

CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; LV, left ventricle; PCI, percutaneous coronary intervention; SD, standard deviation.

the treated lesions involved the left anterior descending-first diagonal (LAD-D1) bifurcation (52%). Considering the protocol requirement of a SB RVD < 2.75 mm, no left main stem lesions were enrolled. According to the DEFINITION criteria,[13] 75% of the treated lesions were deemed as complex.

Intervention details and procedural results

Technical details of the procedure are reported in *Table 2*. The mean diameter of the DES implanted in the MV-MB axis was 2.98 ± 0.49 mm, while the diameter of the DCB in the SB was 2.35 ± 0.36 mm. DCB inflation followed DES implantation in the majority of cases (84%), usually with a kissing uncoated balloon in the MB (80% of the total procedures) (*Table 3*).

Procedural success was achieved in 96% of the cases. In one patient, the DCB was not able to reach the target segment, and the patient was treated with POBA. In the DES-treated segment, %DS improved from 82.9 ± 9.0 to 7.3 ± 3.2 ($P < 0.001$), while in the DCB-treated segment it improved from 81.9 ± 11.7 to 22.9 ± 5.9 ($P < 0.001$) (*Table 4*). No cases of residual stenosis or major dissection requiring an additional stent were recorded.

In-hospital and one-year clinical outcomes

During hospitalization, one case of post-procedural MI and one case of major bleeding were recorded.

At 1 year follow-up, only one case of ID-TLR was recorded, in the DES-treated segment. No other adverse events occurred, and no cases of suspected or definite thrombosis were recorded (*Table 5*).

Table 2 Procedural details

	Lesions ($n = 50$)
Radial access, *n* (%)	42 (84)
Contrast media (mL), mean ± SD	158 ± 60
Fluoroscopy time (min), mean ± SD	23 ± 11
LAD-D1 lesion, *n* (%)	26 (52)
RCA-PDA-PL lesion, *n* (%)	16 (32)
LCx-OM1, *n* (%)	8 (16)
Pre-dilatation (MB and SB), *n* (%)	50 (100)
Pre-dilatation semi-compliant balloon (DCB target segment), *n* (%)	20 (40)
Pre-dilatation non-compliant balloon (DCB target segment), *n* (%)	30 (60)
MB DES diameter (mm), mean ± SD	2.98 ± 0.49
MB DES length (mm), mean ± SD	29.0 ± 9.5
SB DCB diameter (mm), mean ± SD	2.35 ± 0.36
SB DCB length (mm), mean ± SD	22.8 ± 6.9
SB DCB inflation pressures (atm), mean ± SD	10.4 ± 2.1
SB DCB inflation time (s), mean ± SD	60.1 ± 18.4

DCB, drug-coated balloon; D1, first diagonal; DES, drug-eluting stent; LAD, left anterior descending; LCX, left circumflex; MB, main branch; OM1, obtuse marginal; PDA, posterior descending artery; PL, posterolateral branch; RCA, right coronary artery; SB, side branch; SD, standard deviation.

Table 3 Drug-coated balloon fashion at the ide branch using a hybrid strategy

	Lesions ($n = 50$)
SB DCB after MB stenting, *n* (%)	42 (84)
Kissing balloon inflation, *n* (%)	40 (95)
POT-SB DCB-POT, *n* (%)	2 (5)
SB DCB only before MB stenting, *n* (%)	8 (16)

DCB, drug-coated balloon; MB, main branch; POT, proximal optimization technique; SB, side branch.

Discussion

The main findings of this substudy can be summarized as follows: (1) a hybrid strategy consisting in the combination of a DES and a DCB was a feasible and safe option for the treatment of CBL with a small calibre SB; (2) treatment provided a high rate of procedural success, even in complex lesions which may require two-stent strategies in clinical practice; (3) good clinical outcomes persisted at 1 year follow-up, with no events related to DCB-treated segments.

First, a hybrid strategy combining DES and DCB may be a feasible and safe treatment option for true CBL PCI, even in case of complex lesions. DCBs have experienced a significant evolution in terms of deliverability and trackability, and they can be used without significant issues in most cases, even across stent struts or during kissing balloon inflation. In our study, procedural success was achieved in 96% of cases, with only one case of unsuccessful delivery of the DCB to the target segment. As per usual practice with DCB, the hybrid strategy considered acceptable results even cases with minor dissections or not 'stent-like' results in terms of residual stenosis.[9] Still, this strategy was not burdened by a higher rate of adverse events compared to the segment treated with DES. No intraprocedural complications were recorded, and no cases of bailout stenting occurred. During in-hospital stay, one case of peri-procedural MI was detected, which was managed conservatively.

In addition to the safety profile, in our study the hybrid strategy provided good results over time, with only one case of TLR (in a DES-treated segment), and no adverse events related to the DCB inflated in the SB.

These results, along with the 'leaving nothing behind' philosophy associated with the use of DCB, may be an attractive therapeutic option with potential benefits in all subsets of lesions, through the combination of a sustained anti-proliferative effect, the avoidance of an additional stent implantation and a simplification of the procedure.

Provisional strategy is currently the first-line recommendation for CBL treatment (unless a severe stenosis of a larger SB requires an upfront two-stent strategy) and represents the vast majority of CBL PCIs in daily practice. Provisional has improved the outcomes through simplification of the procedure (the so-called 'KISS' principle, i.e. 'keep it simple and safe') and through avoidance of the implantation of a second stent in the bifurcation, if not strictly needed. However, it should be acknowledged

Table 4 Angiographic results at quantitative coronary angiography

	Baseline	Final	*P* value
DES-treated segment (MB)			
RVD (mm), mean ± SD	2.91 ± 5.2		
MLD (mm), mean ± SD	0.44 ± 0.47	1.9 ± 0.6	0.0001
Diameter stenosis (%), mean ± SD	82.9 ± 9.0	7.3 ± 3.2	0.0001
Lesion length (mm), mean ± SD	25.8 ± 7.3		
Acute gain (mm), mean ± SD		1.55 ± 1.2	
DCB-treated segment (SB)			
RVD (mm), mean ± SD	2.3 ± 0.5		
MLD (mm), mean ± SD	0.44 ± 0.32	1.55 ± 0.9	0.0001
Diameter stenosis (%), mean ± SD	81.9 ± 11.7	22.9 ± 5.9	0.0001
Lesion length (mm), mean ± SD	17.7 ± 7.2		
Acute gain (mm), mean ± SD		1.10 ± 0.56	
Target vessel quantitative flow ratio		0.92 ± 0.1	

DCB, drug-coated balloon; DES, drug-eluting stent; MLD, minimal lumen diameter; RVD, reference vessel diameter; SB, side branch; SD, standard deviation.

Table 5 Clinical, in-hospital and 1 year outcomes

	n = 50
In-hospital outcome	
Procedural success, *n* (%)	48 (96)
Peri-procedural MI, *n* (%)	1 (2)
Raise in cardiac biomarkers (>5 times the normal upper limit)	4 (8)
Flow-limiting dissection requiring stenting, *n* (%)	0 (0)
DCB did not reach the target lesion, *n* (%)	1 (2)
Major bleeding (according BARC classification), *n* (%)	1 (2)
1 Year outcome	
Device-oriented composite endpoint, *n* (%)	1 (2)
Cardiac death, *n* (%)	0 (0)
Target vessel MI (excluding periprocedural MI), *n* (%)	0 (0)
Overall ID-TLR, *n* (%)	1 (2)
ID-TLR DES target segment, *n* (%)	1 (2)
ID-TLR DCB target segment, *n* (%)	0
Thrombosis at the SB DCB or MB DES	0 (0)

BARC, Bleeding Academic Research Consortium; DCB, drug-coated balloon; DES, drug-eluting stent; ID-TLR, ischemia-driven target lesion failure; MB, main branch; MI, myocardial infarction; SB, side branch.

that even in the absence of a significant stenosis, plaque often involves the SB. In provisional, both proximal optimization (POT) and kissing balloons dilate the SB ostium, but there is no direct effect to prevent intima hyperplasia, plaque progression and restenosis, as plain uncoated balloons are used. Indeed, balloon inflation may even cause endothelium damage, which is an established trigger of intimal proliferation. Hereby, the local administration of an anti-proliferative drug may find a sound rationale in the prevention of future plaque progression and restenosis at the SB level, which remains the weak spot of any bifurcation PCI, regardless of the strategy of choice.

Moreover, these findings may apply also to two-stent strategies, as a DCB may avoid the deployment of a second stent in the bifurcation, with potential benefits both in terms of simplification of the procedure and of reduction of overlapping metal struts. Of note, the 2.75 mm limit in SB RVD applied in the HYPER study may select lesions more amenable of a provisional strategy, but 76% of CBL met the DEFINITION criteria for complex lesions,[13] which in the DEFINITION II trial[14] achieved better long-term result with an upfront two-stent strategy compared to provisional (TLF rate of 6.1% vs. 11.4%, respectively, *P* 0.019; hazard ratio 0.52). In the DEFINITION II trial, the SB RVD had to be ≥2.5 mm, but the majority of implanted DES were <2.75 mm. Thus, a certain overlap between the two-study populations exists (2.64 ± 0.3 mm vs. 2.35 ± 0.36 mm of DES and DCB diameter in the DEFINITION II and HYPER study, respectively), although a direct comparison cannot be performed.

Other studies tried to assess the impact of a hybrid strategy, or even a full-DCB strategy, in the setting of CBL. However, the available evidence is characterized by heterogeneous methodologies, with no randomized controlled trials, and significant differences in the type of CBL (i.e. different Medina classification) and treatment strategy, both in terms of target of the DCB inflation and order of the treatment (i.e. DCB before or after DES implantation). Among these studies, the most relevant results suggested a better outcome in terms of restenosis or late lumen loss with a DCB in the SB compared to POBA.[15,16] Two meta-analyses[17,18] confirmed these results showing a consistent superiority in terms of late lumen loss for DCB. However, the lack of randomized controlled trials and the small population affected statistical power and quality of data, thus preventing any conclusions on clinical endpoints.

Moreover, critical heterogeneity across studies was detected in lesion preparation. Some bifurcation papers[19] did not follow current criteria and recommendations,[9] although optimal preparation has emerged as the most critical point for the long-term success of DCB. The HYPER study required an effective pre-dilatation of all lesions before DCB treatment and this allowed a 100% rate of procedural success in those subjects where the DCB was

effectively delivered to the target segment. In general, the HYPER is the first study to apply a standardized, robust and up-to-date protocol for the application of DCB and hybrid strategies in the setting of bifurcation PCI.

In our opinion, despite the limited sample size, these results should warrant larger, randomized controlled trials to compare the outcomes of this treatment with standard provisional strategy and two-stent strategies.

Limitations

Although our study involved one of the largest populations and robust methodologies available in the field of CBL PCI and DCB, it is still a small, observational study. Adequately sized randomized controlled trials are necessary to gather more robust evidence. Although we relied on an expert, external core-lab for QCA, intracoronary imaging may provide more detailed information about lesion preparation and procedural results. Additional standardization of the procedural steps of the hybrid strategy may reduce bias and further improve data quality. No angiographic follow-up was planned per protocol, so no data are available on the rate of 'silent' restenosis at 1 year; still, the absence of symptoms or of adverse events are good indicators of the sustained success of the revascularization.

Conclusions

A hybrid strategy for true CBL treatment, employing a DES for the treatment of the MV–MB axis, and a DCB for the SB, may be a safe and effective procedure, with persistence of good clinical outcomes at 1 year follow-up. Additional, randomized studies are warranted to compare the outcomes of this hybrid strategy to traditional treatment.

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Data availability

Anonymized patient-level data are available upon reasonable request to the corresponding authors.

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