DOI: 10.1111/joic.12333

PERCUTANEOUS CORONARY INTERVENTION

Drug-Coated Balloons: A Safe and Effective Alternative to Drug-Eluting Stents in Small Vessel Coronary Artery Disease

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***Background**: Drug-coated balloons (DCB) have been used to treat de novo small vessel coronary disease (SVD), with promising results and shorter dual antiplatelet therapy (DAPT) duration compared to drug-eluting stents (DES). We compared safety and effectiveness of the two treatments at 1 year.*
***Methods**: We reviewed 3,613 angioplasty cases retrospectively from 2011 to 2013 and identified 335 patients with SVD treated with device diameter of ≤2.5 mm. DCB-only angioplasty was performed in 172 patients, whereas 163 patients were treated with second-generation DES.*
***Results**: DCB patients had smaller reference vessel diameter (2.22 ± 0.30 vs. 2.44 ± 0.19 mm, P < 0.001) and received smaller devices (median diameter 2.25 vs. 2.50 mm, P < 0.001) compared to the DES group. DES-treated vessels had larger acute lumen gain (1.71 ± 0.48 mm) than DCB (1.00 ± 0.53 mm, P < 0.001). Half the patients had diabetes mellitus. While there were more patients presenting with acute coronary syndrome (ACS) in the DCB group (77.9% vs. 62.2%, P = 0.013), they received shorter DAPT (7.4 ± 4.7 vs. 11.8 ± 1.4 months, P < 0.001) than the DES group. The 1-year composite major adverse cardiac event rate was 11.6% in the DCB arm and 11.7% in the DES arm (P = 1.000), with target lesion revascularization rate of 5.2% and 3.7%, respectively, (P = 0.601).*
***Conclusions**: In this high-risk cohort of patients, DCB-only angioplasty delivered good clinical outcome at 1 year. The results were comparable with DES-treated patients, but had the added benefit of a shorter DAPT regime.* (J Interven Cardiol 2016;29:454–460)

Introduction

Coronary stents were introduced to overcome inherent limitations of balloon angioplasty, namely, dissection, elastic recoil, and frequent requirement for repeat intervention.[1,2] Early bare metal stents (BMS) were plagued by high rates of restenosis, a process which has largely been mitigated by improved stent design (allowing reduction in strut thickness) and application of an anti-proliferative agent designed to arrest neointimal hyperplasia.[3] Such drug-eluting stents (DES) have become the primary mode of coronary revascularization, achieving excellent early and long-term success in the majority of patients.[3,4] However, small coronary arteries (<2.5 mm) remain a particular challenge with high rates of stent failure due to late lumen loss (LLL) and may predict both repeat revascularization and subsequent adverse events.[5]

Drug-coated balloons (DCB) have recently emerged as a potential therapeutic strategy for patients with small vessel de novo coronary artery disease,[6,7] even in the setting of primary angioplasty.[8] DCB allow rapid and uniform tissue delivery of paclitaxel to the lesion of interest and is an established treatment modality for in-stent restenosis.[9] In de novo disease, a DCB strategy allows stent-free revascularization, thereby removing the detrimental effect of metal from the equation that drives LLL.[2]

Conflict of interest: All authors report no conflict of interest.

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There is presently limited data evaluating the routine use of DCB in de novo small vessel disease. This study was designed to report the safety and efficacy of this technology in comparison to a cohort of second-generation DES in real-world clinical practice.

Methods

Data Collection. Tan Tock Seng Hospital is one of the largest providers of acute and elective cardiac care in Singapore and an experienced DCB center (approximately 20% of all PCI per annum). From our coronary angioplasty database, patients with small vessel disease treated between January 2011 and December 2013 with a final device diameter $\leq$2.5 mm were identified. Based on the treatment, the samples were divided into DCB- (all SeQuent Please paclitaxel-coated balloon, B-Braun, Melsungen, Germany) and DES-treated groups. All patients were followed up for a minimum of 1 year.

All demographic and procedural data were collected and analyzed. Data were extracted from our electronic medical record, which serves for comprehensive data capture within not only our own institution but also at all other publicly funded health care facilities in Singapore and is supplemented with data from mandatory national statistical collection. Each coronary angiogram and associated procedural event log were also carefully reviewed to determine lesion characteristics and PCI technique.

Definitions. The following definitions were used in this study: Diabetes mellitus—fasting blood glucose >7 mmol/L, random blood glucose >11.1 mmol/L, HbA1c >7%, or preexisting use of oral hypoglycemic agents or insulin; dyslipidemia—total cholesterol >5.2 mmol/L, LDL >2.6 mmol/L, or prescription of drugs to target dyslipidemia; hypertension—systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or preexisting use of antihypertensive drugs; renal failure—Cockcroft–Gault creatinine clearance <50 mL/min or undergoing dialysis; acute coronary syndrome/myocardial infarction (ACS/MI)—evidence of myocardial necrosis consistent with the third International Definition of Myocardial Infarction[10]; MACE consisting of death (all-cause), recurrent MI, and repeat revascularization at 12 months, as per the Academic Research Consortium (ARC) definition.[11]

Data Analysis. Following a test of distribution with Kolmogorov–Smirnov test, data were described as mean $\pm$ standard deviation or median (quartiles) as appropriate. Categorical variables were evaluated with the Chi-square test, whereas continuous variables were compared with the unpaired two-tailed Student's *t*-test or Mann–Whitney *U*-test. We performed univariate Cox regression analysis on demographics, risk factors, and procedural and intervention data to determine factors independently associated with 1-year MACE. Multivariate Cox regression was used to adjust for baseline differences and all MACE-associated variables with a P-value <0.2. Hazard ratio (HR) and 95% confidence interval (CI) are presented. Kaplan–Meier curves are presented for each treatment group and are compared using the log-rank test. SPSS version 20.0 (IBM, Armonk, NY, USA) was used for all analyses at a significance level of 0.05.

Results

A total of 335 patients (mean age 61.1 $\pm$ 11.0 years old, 74% male), with 390 lesions were identified as meeting inclusion criteria for this study. Of these, DCB was used in 172 patients (194 lesions) and 163 (196 lesions) patients received DES (Table 1). Approximately 50% (188 patients) of all patients had diabetes mellitus. There was no significant difference in baseline demographics or comorbidities (e.g., hypertension, hyperlipidemia, etc.) between the two groups. A higher rate of current or recent smoking was reported among the DCB cohort (44.8% vs. 30.2%, P = 0.006).

Approximately 72% (134 patients) of the patients had presented to hospital with an ACS, of which 39% (94 patients) represented primary PCI for acute ST-segment elevation myocardial infarction. The remainder presented with stable angina pectoris. ACS was a more common presenting feature in the DCB compared to DES group (77.9% vs. 62.2%, P = 0.013).

The most commonly treated vessel was the left anterior descending artery (41.2%), followed by the left circumflex artery (33.2%) and the right coronary artery (24.8%). The distributions of target vessels were broadly similar in both groups. Numerically, more branch lesions (diagonal, obtuse marginal, posterolateral, or posterior descending artery) were treated with DCB (20.9% vs. 11.0%), while more proximal lesions were treated with DES (17.4% vs. 23.9%, P = 0.074 for DCB vs. DES, respectively).

Table 1. Demographics of Study Population (N = 335)

Variable	Drug-Coated Balloon (n = 172)	Drug-Eluting Stent (n = 163)	P-Value
Male (n, %)	132 (76.7)	117 (71.8)	0.298
Age (mean ± SD, years old)	61.0 ± 11.8	61.2 ± 10.7	0.877
Diabetes mellitus (n, %)	88 (51.2)	80 (49.1)	0.703
Hypertension (n, %)	125 (72.7)	113 (69.3)	0.499
Hyperlipidemia (n, %)	120 (69.8)	118 (72.4)	0.596
Smoker (n, %)	52 (30.2)	73 (44.8)	0.006
Presentations			
Acute coronary syndrome (n, %)	134 (77.9)	107 (62.2)	0.013
Indication			0.031
Stable angina (n, %)	38 (22.1)	56 (34.4)	
Unstable angina pectoris/non-ST segment elevation MI (n, %)	85 (49.4)	62 (38.0)	
ST segment elevation MI (n, %)	49 (28.5)	45 (27.6)	
Procedural data			
Number of lesions (median, Quartiles)	1 (1–1)	1 (1–1)	0.084
1 (n, %)	151 (87.8)	132 (81.0)	
2 (n, %)	20 (11.6)	29 (17.8)	
3 (n, %)	1 (0.6)	2 (1.2)	
Number of devices (median, Quartiles)	1 (1–2)	1 (1–2)	0.696
1 (n, %)	116 (67.4)	115 (70.6)	
2 (n, %)	48 (27.9)	36 (22.1)	
3 (n, %)	8 (4.7)	9 (5.5)	
4 (n, %)	0 (0.0)	3 (1.8)	
Reference diameter (mean ± SD, mm)	2.22 ± 0.30	2.44 ± 0.19	<0.001
Device diameter (median, Quartiles, mm)	2.25 (2–2.5)	2.5 (2.25–2.5)	<0.001
Device length (mean ± SD, mm)	20.20 ± 6.04	22.22 ± 7.22	0.006
Acute luminal gain (mean ± SD, mm) by quantitative coronary angiography	1.00 ± 0.53	1.71 ± 0.48	<0.001
Type C lesion (n, %)	73 (42.4)	65 (37.8)	0.634
Chronic total occlusion (n, %)	2 (1.2)	2 (1.2)	1.000
Vessel			0.848
Left anterior descending artery (n, %)	71 (41.3)	67 (41.1)	
Left circumflex coronary artery (n, %)	55 (32.0)	56 (34.4)	
Right coronary artery (n, %)	45 (26.2)	38 (23.3)	
Ramus intermedius (n, %)	1 (0.6)	2 (1.2)	
Location			0.074
Proximal (n, %)	30 (17.4)	39 (23.9)	
Mid (n, %)	72 (41.9)	73 (44.8)	
Distal (n, %)	34 (19.8)	32 (19.6)	
Other/branches (n, %)	36 (20.9)	18 (11.0)	

MI, myocardial infarction.

The majority of patients had a single lesion treated (87.8% in DCB vs. 81.0% in DES, P = 0.084) and in the majority only one device was required (67.4% in DCB vs. 70.6% in DES, P = 0.696). There was no significant difference in the complexity of the lesions (B2/C lesions, 42.4% DCB vs. 37.8% DES, P = 0.63). The reference vessel diameter (2.22 ± 0.30 vs. 2.44 ± 0.19 mm, P < 0.001), device diameter (median

Table 2. Distribution of Dual Antiplatelet Therapy in DCB and DES Groups

Variable	Drug-Coated Balloon (n = 172)	Drug-Eluting Stent (n = 163)	P-Value
Types of DAPT			0.180
Aspirin alone (n, %)	0 (0.0)	0 (0.0)	
DAPT with clopidogrel (n, %)	162 (94.2)	149 (91.4)	
DAPT with prasugrel (n, %)	6 (3.5)	13 (8.0)	
DAPT with ticagrelor (n, %)	3 (1.7)	1 (0.6)	
Aspirin plus warfarin (n, %)	1 (0.6)	0 (0.0)	
Duration of DAPT (median, Quartiles; months)	6 (3–12)	12 (12–12)	<0.001

DAPT, dual antiplatelet therapy.

2.25 [2–2.5] vs. 2.5 [2.25–2.5] mm, $P < 0.001$), and device length (20.2 ± 6.0 vs. 22.2 ± 7.2 mm, $P = 0.006$) for DCB versus DES respectively, reflecting the nature and position of lesions treated. Acute luminal gain was significantly greater in the DES group compared with the DCB group (1.71 ± 0.48 vs. 1.00 ± 0.53 mm, $P < 0.001$).

All DCB devices were Sequent Please (B. Braun Melsungen Germany). DES usage was 33.7% zotarolimus (Resolute Integrity, Medtronic Vascular, Inc., USA), 32.5% everolimus (Xience, Abbott Vascular USA or Promus Element, Boston Scientific, MA, USA), and 32.5% biolimus (Biomatrix, Biosensors International SG and Nobori, Terumo, Japan).

All patients received aspirin (300 mg loading prior to procedure, 100 mg daily maintenance). Thienopyridine usage was primarily clopidogrel (94.2% DCB vs. 91.4%, $P = 0.18$). The remainder received prasugrel or ticagrelor. Median thienopyridine duration was 6 (3–12) months versus 12 (12–12) months, $P < 0.001$ for DCB versus DES, respectively (Table 2).

At the 1-year follow-up, there were 20 (11.6%) composite MACE events in the DCB arm—with three (1.7%) deaths, 10 (5.8%) myocardial infarctions, and nine (5.2%) TLRs (Table 3 and Fig. 1). In the DES arm, there were 19 (11.7%) composite MACE, six (3.68%) deaths, 14 (8.6%) myocardial infarctions, six (3.7%) TLRs, and one (0.6%) stroke event.

Univariate Cox regression analysis revealed that diabetes mellitus type II (HR 2.0, $P = 0.038$), device length (HR 1.0, $P = 0.005$), type B2/C lesion (HR 2.7, $P = 0.003$) were significantly associated with composite MACE (Table 4). There was no selection for device type in both univariate and multivariable analysis. Multivariable analysis did not reveal any factor that had significant predictive value for 1-year MACE (Table 5).

Discussion

Our study indicates that DCB appeared to be a viable alternative to DES for treatment of patients with de novo small vessel coronary artery disease. Procedural outcome was good with both strategies and low MACE event rates were reported at 12 months, particularly among those patients treated with DCB. These findings are largely in keeping with other published series. The

Table 3. Clinical Outcomes at 1 Year

Variable	Drug-Coated Balloon (n = 172)	Drug-Eluting Stent (n = 163)	P-Value
Composite MACE (n, %)	20 (11.6)	19 (11.7)	1.000
Death (n, %)	3 (1.7)	6 (3.7)	0.326
Myocardial infarction (n, %)	10 (5.8)	14 (8.6)	0.398
Target lesion revascularization (n, %)	9 (5.2)	6 (3.7)	0.601
Cerebrovascular accident (n, %)	2 (1.2)	1 (0.6)	1.000

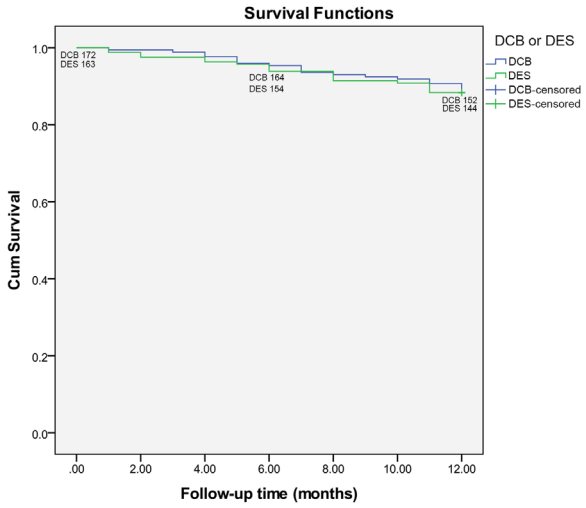

Figure 1. Kaplan–Meier curve in drug-coated balloon- and drug-eluting stent-treated patients over a follow-up period of 1 year. There was no difference in survival from major adverse cardiac events between the two groups during the observation period.

prospective BELLO (Balloon Elution and Late Loss Optimization) study,[7] showed that DCB was associated with less angiographic late (6 month) lumen loss (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; P-value (superiority) $= 0.001$), and similar rates of restenosis (10% vs. 14.6%; $P = 0.35$) and revascularization (4.4% vs. 7.6%; $P = 0.37$) compared to paclitaxel-eluting DES in treating SVD.[12] Similarly, the prospective PEPCAD I study showed that DCB angioplasty with Paccocath technology DCB in SVD demonstrated good 6-month angiographic and 12-month clinical outcome and reported a DCB TLR rate of 4.9% at 12 months.[13]

As anticipated, DES in the present study tended to be more often used in proximal lesions within the major epicardial coronary arteries. DCB usage was more variable and in addition to use in major epicardial vessels, frequently included branch vessels. These latter lesions were almost exclusively treated using a DCB strategy. The anatomical difference between the two strategies is an important consideration. Small vessels and side-branches are often left for medical therapy as metallic stents within small vessels frequently have poor outcome due to LLL. For example, one meta-analysis compared outcome with BMS versus balloon angioplasty alone for small vessel disease and reported a 1-year TLR rate of 12.5% versus 17%, respectively.[14] Following introduction of DES, outcomes in small vessels have dramatically improved, although remain far below performance expected when DES is utilized in larger vessels. One such study reported a 6-month target vessel revascularization (TVR) rate of 3.9 versus 9.2% ($P = 0.007$) and 3-year TVR rate of 13.8 versus 18.0% ($P = 0.043$) for first-generation DES versus BMS, respectively, with devices ≤ 2.25 mm.[15] Subsequent generation DES yielded improved results, for example, the SPIRIT

Table 4. Results of Univariate Cox Regression Analysis to Evaluate Predictors of 1-Year Composite Major Adverse Cardiac Events

	Univariate analysis		
Variable	Hazard Ratio	95% Confidence Interval	P-Value
Device (DCB or DES)			
DCB	Reference		
DES	1.013	0.541–1.898	0.968
Age	1.023	0.995–1.051	0.104
Gender			
Female	0.994	0.484–2.039	0.987
Male	Reference		
Diabetes mellitus type II			
With	2.024	1.040–3.938	0.038
Without	Reference		
Hypertension			
With	1.605	0.738–3.491	0.233
Without	Reference		
Hyperlipidemia			
With	1.903	0.852–4.372	0.115
Without	Reference		
Smoker			
Yes	0.741	0.376–1.464	0.389
No	Reference		
Reference luminal diameter	1.610	0.504–5.144	0.421
Device size	1.765	0.300–10.388	0.530
Device length	1.060	1.018–1.107	0.005
Acute luminal gain	0.892	0.533–1.493	0.664
Type C lesion			
With	2.659	1.382–5.115	0.003
Without	Reference		
Acute coronary syndrome	1.139	0.555–2.338	0.722
Number of lesions	0.945	0.417–2.140	0.891
Number of devices	1.153	0.725–1.831	0.548

DCB, drug-coated balloon; DES, drug-eluting stent.

Table 5. Results of Multivariable Cox Regression Analysis to Evaluate Predictors of 1-Year Composite Major Adverse Cardiac Events

	Multivariate Analysis		
Variable	Hazard Ratio	95% Confidence Interval	P-Value
Device (DCB or DES)*			
DCB	Reference		
DES	1.032	0.438–2.432	0.943
Age*	1.022	0.991–1.054	0.175
Diabetes mellitus type II*			
With	1.709	0.832–3.508	0.144
Without	Reference		
Hyperlipidemia*			
With	1.439	0.604–3.424	0.411
Without	Reference		
Device length*	1.032	0.974–1.094	0.286
Type C lesion*			
With	2.020	0.890–4.584	0.093
Without	Reference		

*Smoker, acute coronary syndrome, indication, reference luminal diameter, device size, and acute luminal gain were used as covariates in the model.

Small Vessel Trial reported a clinically driven TLR rate of 5.1% at 1 year.[16] However, it is clear that results with small vessel DES remain far from ideal and continue to require an extended DAPT regimen.

In contrast to a stent strategy, DCB relies on the concept of progressive positive remodeling. Following careful and controlled balloon angioplasty, paclitaxel at a concentration of around 3 mcg/mm^2 is delivered using a lipophilic carrier agent, which allows the drug to be rapidly dispersed from DCB into the arterial wall. Paclitaxel acts to inhibit progressive smooth muscle proliferation and endothelial hyper-proliferation, which if combined with dissection, were the Achilles heel of balloon angioplasty. Naturally, due to the absence of a stent, elastic recoil is more notable and acute lumen gain less substantial with DCB as compared to DES. Of intrigue, several anecdotal studies, which have documented follow-up angiography, have suggested that DCB may have progressive lumen gain over time.[2] Should sustained results be achieved routinely, this would yield potential advantage for DCB over DES by removing the metallic cage which may provide a platform to induce localized inflammation and which may in turn drive LLL and mandate prolonged DAPT. This latter point could in part explain why there was lower MACE in the present study. It is well known that metallic DES inhibits endothelialization, potentially predisposing to stent thrombosis. Therefore, the absence of metal and polymer may allow the artery to "heal" more rapidly following DCB, removing substrate for adverse events. This effect may be exaggerated should patients with DES have been less compliant or only partial responders to DAPT therapy. However, an equally plausible explanation is that anatomical lesion location may influence the prognosis and it is therefore possible that smaller side branches may not influence MACE to the same degree as a major epicardial vessel. Not all DCBs are the same and as to reduce confounding factors, only SeQuent Please DCB outcome was evaluated in this report. In our practice, all DCB-treated patients were firstly prepared by using compliant, non-compliant, or scoring balloons to achieve good balloon angioplasty result: minimal residual stenosis (<30%) without any occluding, or type C or above dissection. Predilatation was done on a 1:1 balloon to artery ratio basis and the decision to treat with DCB was only made after initial predilatation. Our previous published study on DCB angioplasty revealed only 4% of the patients required bailout stenting for significant recoil/dissection (>type B dissection).[8]

Limitations

This is a small retrospective observational study, with initial treatment choice entirely at operator discretion. There is significant mismatch between lesion locations. Anti-platelet regimens were not matched. There is an absence of angiographic follow-up.

The study was aimed to compare the MACE between groups, and was not powered to demonstrate bleeding risk. However, it is reasonable to expect lower bleeding rate in the group with shorter DAPT period as already dictated by other previous studies.[17]

Conclusion

In the present study, DCB to treat de novo small vessel coronary disease appeared to be both safe and effective in this group of high-risk patients, with

procedural outcomes that compare favorably with published data of second-generation DES. We propose that DCB is a viable alternative to DES in treating small vessel coronary disease. Large randomized studies need to be initiated.

Acknowledgments: We would like to thank Dr. Yoko Wong Kin Yoke and Ms. Sun Bing for their statistical assistance and Ms. Safiyya Mohamed Ali for her editorial assistance.

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