Major adverse cardiac events and drug-coated balloon size in coronary interventions

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Abstract

Objective: In-stent restenosis (ISR) is a feared complication after coronary stent implantation. Drug-coated balloon (DCB) is being promoted as a treatment option for ISR. However, the benefit-risk ratio of DCB length has not been investigated. Longer DCBs release more anti-proliferative drug to the vessel wall; however, they are associated with a higher lesion length and vessel injury. Hypothesis: DCB length is associated with clinical outcome.

Methods: We analyzed 286 consecutive Pantera Lux (Biotronik, active component Paclitaxel) DCB-treated patients between April 2009 and June 2012. Of them, 176 patients were treated using a 15-mm DCB and 109 were treated using a 20-mm DCB. Baseline characteristics and major adverse cardiac events (MACE; death, myocardial infarction, and target lesion revascularization) during initial hospital stay and a 2-year follow-up period were obtained.

Results: Patients characteristics such as cardiovascular risk factors, prior diseases, co-medication, clinical presentation, target vessel, and left ventricular function did not differ between the groups. MACE during hospital course was similar [1.7% vs. 2.8%, relative risk (RR) 1.6, 95% confidence interval (CI) 0.3-7.9, p=0.554]. Likewise, at 2-year follow-up, MACE did not differ between the groups (23.2% vs. 27.5%, RR 1.2, 95% CI 0.6-1.5, p=0.408).

Conclusion: DCB length was not associated with clinical outcome during a 2-year follow-up period. *(Anatol J Cardiol 2018; 19: 382-7)*

Keywords: drug-coated balloon, drug-eluting stent, MACE, paclitaxel

Introduction

The treatment of coronary artery disease was revolutionized by balloon angioplasty and stent implantation. However, common complications observed after coronary stent implantation are stent thrombosis, myocardial infarction (MI), and repeated need for revascularization (1). Stent thrombosis is particularly associated with a substantially increased (up to 30%) risk of death (2). Among other factors, a strong independent risk factor for major adverse cardiac events (MACE) is stent length. Stent length is associated with stent thrombosis, death, MI, and target lesion revascularization (TLR) (3-5). Besides acute adverse events, restenosis due to neointimal growth is still a major concern after stent implantation (6). After 5 years, 10% of drug-eluting stent-treated patients and 20%-30% of bare-metal stent treated patients experience in-stent restenosis (ISR) with need for repeat revascularization (7, 8). Drug-coated balloon (DCB) angioplasty is a promising treatment for ISR (8-11). DCB are semi-compliant and covered with an anti-proliferating drug; during angioplasty, they release this active agent into the vessel wall (12). However, it is not known whether DCB length is associated with clinical outcome. Longer DCBs are used in larger lesions as they release more anti-proliferative drug into the vessel wall; however, they cause more vessel injury. In this study, we conducted a hypothesis-generating pilot analysis of the Düsseldorf DCB registry. We aimed to associate DCB length and clinical outcome during hospital course and a 2-year follow-up.

Methods

Study design, patient population, follow-up

Data of 286 paclitaxel DCB (Pantera Lux, BIOTRONIK, SE & Co.KG, Berlin, Germany)-treated patients of the Düsseldorf DCB registry were analyzed in a retrospective manner. Of all the patients, 176 (61.8%) were treated using a 15-mm and 109 (38.2%)

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were treated using a 20-mm Pantera Lux DCB between April 2009 and June 2012. Quantitative coronary stenosis assessment (QCA) was not performed, and the lesion length was estimated regarding the pre-dilatation parameters by an interventionalist. DCB inflation was performed, and inflation duration and pressure were registered and compared between the groups.

Follow-up was conducted during ambulatory care at the Cardiology Department of the Heinrich-Heine-University Clinic Düsseldorf (Düsseldorf, Germany). The analysis was approved by the Ethics Committee of the Heinrich-Heine-University Düsseldorf (Düsseldorf, Germany).

Study endpoints

The incidences of TLR, MI, and all-cause death were investigated during hospital course and at 2-year follow-up appointment. Signs of ischemia, elevation of cardiac enzyme levels, and angiographically proven culprit lesion defined MI. Repeated revascularization of the DCB target lesion without meeting MI criteria was defined as TLR.

Statistical analysis

Statistical analysis was performed using IBM SPSS©-Software (New York, USA) and GraphPad Prism statistical software (GraphPad Software Inc, San Diego). Calculation of relative risk (RR) with 95% confidence interval (CI) was done according to Altman (13). Hazard ratios (HRs) with 95% CI and log-rank test were used in MACE analysis. Normal distribution was tested using histograms, QQ-plots, and Kolmogorov-Smirnov test. Gaussian-distributed continuous variables were analyzed using t-test. Non-normally distributed variables were assessed using Mann-Whitney U test. Categorical variables were analyzed using Fisher's exact and x^2 tests as applicable. All tests were two tailed, and $p<0.05$ was considered significant. This was a hypothesis-generating explorative analysis; therefore, no power calculation was conducted.

Results

Baseline characteristics

Mean age of the study population was 73±10 years; 121 (68.4%) patients were male. Gender and body mass index (27±5 vs. 28±5; p=0.368) did not differ between the groups. Likewise, there were no significant differences between the groups regarding cardiovascular risk factors, medical history, clinical presentation, left ventricular function, or medication at discharge. Detailed baseline characteristics are illustrated in Tables 1 and 2 and Supplemental 1.

Table 1. Patients characteristics

	15 mm n=177	20 mm n=109	*P*-value*
Characteristics			
Age, years (mean ± SD)	73±10	73±10	0.670
Male gender, no. (%)	121 (68.44%)	83 (76.1%)	0.121
Height, cm (mean ± SD)	174±9	171±9	0.622
Weight, kg (mean ± SD)	82±18	81±17	0.279
Body mass index, kg/m^2 (mean ± SD)	27±5	28±5	0.368
Cardiovascular risk factors, no. (%)			
Hypertension	177 (100%)	109 (100%)	>0.999
Hypercholesterolemia	168 (95%)	105 (96%)	0.771
Diabetes mellitus	58 (33%)	44 (40%)	0.212
Current smokers	58 (33%)	28 (26%)	0.225
Obesity (BMI >30 kg/m^2)	39 (22%)	26 (24%)	0.771
Medical history, no. (%)			
Prior myocardial infarction	74 (42%)	50 (46%)	0.536
Prior CABG	30 (17%)	21 (19%)	0.642
Prior stroke	10 (6%)	7 (6%)	0.801
Chronic kidney disease	52 (29%)	30 (28%)	0.788
Dialysis	5 (3%)	2 (2%)	0.707

*_P_-value of Fischer's exact and x^2 tests in categorical variables and t-test in continuous variables; BMI - body mass index; CABG - coronary artery bypass surgery

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Table 2. Clinical presentation and systolic left ventricular function

	15 mm n=177	20 mm n=109	*P*-value*
Presentation, no. (%)			
ST-elevation myocardial infarction	8 (5%)	2 (2%)	0.331
Non-ST-elevation myocardial infarction	27 (15%)	21 (19%)	0.423
Instable angina pectoris	62 (35%)	35 (32%)	0.699
Stable coronary artery disease	70 (40%)	35 (32%)	0.208
CCS-Stadium			0.944
CCS 0	60 (34%)	38 (35%)	
CCS I	18 (10%)	11 (10%)	
CCS II	35 (20%)	16 (15%)	
CCS III	25 (14%)	12 (11%)	
CCS IV	39 (22%)	32 (29%)	
NYHA-Stadium			0.123
NYHA I	77 (44%)	50 (46%)	
NYHA II	53 (30%)	38 (35%)	
NYHA III	32 (18%)	19 (17%)	
NYHA IV	15 (8%)	2 (2%)	
Left ventricular function, no (%)			
Normal	95 (54%)	60 (55%)	0.902
Mildly decreased	37 (21%)	28 (26%)	0.377
Moderately decreased	25 (14%)	10 (9%)	0.260
Severely decreased	20 (11%)	11 (11%)	0.851

*P-value of Fischer's exact and x^2 tests; CAD - coronary artery disease; CCS - Canadian Cardiovascular Society; NYHA - New York Heart Association

DCB intervention

DCB procedure was successfully performed in 278 (97.5%) cases. Mean inflation duration was 50.2±12 s, and mean inflation pressure was 10.53±3.7 atm. There were no differences regarding inflation pressure and duration between the groups. Vessel dissection was seen in 21 (7.4%) patients. Overall, the left anterior descending artery was the predominant target vessel (42% vs. 34%, p=0.320). BMS-ISR was the most common cause for DCB intervention (46% vs. 51%, p=0.472). Bifurcation lesions were significantly more often treated using a 15-mm DCB (15% vs. 2%, p<0.001). Vessel dissection incidence, inflation pressure, inflation duration, and vessel diameter was similar in both groups. An additional stent implantation during DCB procedure was seen in 48 (16.8%) cases, and it did not differ between the groups. Procedure-related data has been presented in Table 3 and Supplemental 1. All types of lesions were included (including saphenous graft lesions, n=22). There were no re-conducted DCB interventions after initial DCB interventions in this cohort (Supplemental 2).

Study endpoints

During hospital course, the occurrence of MACE was similar between 15-mm and 20-mm DCB groups [3 patients (1.7%) vs. 3 patients (2.8%), p=0.554)]. Likewise, at 2-year follow-up, MACE did not significantly differ between the groups [41 patients (23.2%) vs. 30 (27.5%), p=0.408; Table 4, Fig. 1]. During follow-up period, one patient died. MACE was predominantly caused by TLR (21.7% of 15-mm DCB-treated patients vs. 22% of 20-mm DCB-treated patients, p=0.925). MI occurred numerically more frequently in 20-mm DCB-treated patients (12.8% vs. 7.3%, p=0.294; Table 4).

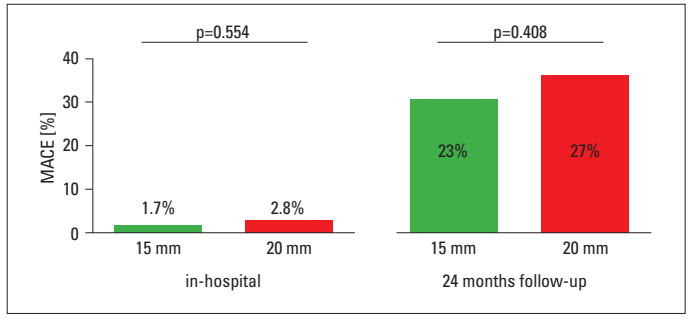

Figure 1. Drug-coated balloon length and MACE. Drug-coated balloon length in coronary intervention was not associated with the incidence of major adverse cardiac events (MACE; death, myocardial infarction, and target lesion revascularization) during hospital stay (a) and at 2-year follow-up (b)

Supplemental 1. Medication

	15 mm n=177	20 mm n=109	*P*-value*
Medication – no. (%)			
Aspirin	161 (91%)	104 (95%)	0.24
P2Y12 inhibitor	172 (97%)	108 (99%)	0.41
Oral anticoagulation	41 (23%)	16 (15%)	0.09
ACE- /AT-II-receptor- inhibitor	153 (86%)	95 (87%)	0.86
Beta- blocker	147 (83%)	97 (89%)	0.23
Calcium- channel inhibitor	46 (26%)	28 (26%)	0.95
Aldosterone antagonist	20 (11%)	12 (11%)	0.94
Cardiac glycoside	15 (8%)	5 (5%)	0.24
Proton-pump inhibitor	59 (33%)	36 (33%)	0.96
Statin	147 (83%)	98 (90%)	0.12
Oral antidiabetic	35 (20%)	19 (17%)	0.64
Insulin	14 (8%)	12 (11%)	0.4
Allopurinol	32 (18%)	22 (20%)	0.76
NSAID	2 (1%)	1 (1%)	0.86
Dipyrone	3 (2%)	4 (4%)	0.43
Morphine	10 (6%)	3 (3%)	0.38

**P*-value of Fischer's exact test and Chi-squared test; ACE – angiotensin-converting-enzyme; AT – angiotensin; NSAID – non steroidal anti inflammatory drug

Supplemental 2. Target vessel and drug-coated balloon indication

	15 mm n=177	20 mm n=109	*P*-value*
Target vessel – no. (%)			
Left anterior descending	75 (42%)	38 (34%)	0.320
Left circumflex	36 (20%)	28 (26%)	0.311
Right coronary artery	49 (27%)	35 (32%)	0.425
Venous bypass graft	15 (8%)	7 (6%)	0.649
Ramus intermedius	2 (1%)	1 (1%)	0.863
Indication – no. (%)			
BMS ISR	82 (46%)	56 (51%)	0.472
DES ISR	43 (24%)	30 (27%)	0.570
Bifurcation	**26 (15%)**	**2 (2%)**	**<0.001**
De-novo lesion	19 (11%)	16 (15%)	0.362
Others	7 (4%)	5 (5%)	0.774

**P*-value of Fischer's exact test and Chi-squared test; BMS – bare metal stent; DES – drug eluting stent

Discussion

The major finding of this pilot analysis was that DCB length is not associated with MACE.

By now, it is well known that coronary stent length is a predictor for outcome for ISR (3-5). Enhanced stent length is associated with more vascular injury as well as increased platelet activation and higher risk of stent thrombosis (14). At the moment, either a DCB angioplasty or a percutaneous coronary intervention with everolimus-eluting stents (that gives best angiographic and clinical

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Table 3. Drug-coated balloon procedure

	15 mm n=177	20 mm n=109	*P*-value*
Balloon (mean±SD)			
Diameter (mm)	3.04±0.6	3.06±0.7	0.783
Inflation pressure (atm)	10.15±3.2	10.90±4.1	0.087
Inflation duration (s)	49.83±12	50.56±12	0.621
Vessel dissection, no. (%)	13 (7%)	7 (6%)	0.820
Combinations, no (%)			
DCB only	145 (82%)	93 (85%)	0.508
DCB+Bare metal stent	16 (9%)	8 (7%)	0.659
DCB+Drug eluting stent	16 (9%)	8 (7%)	0.660
Procedural result, no. (%)			
Angiographic success	173 (98%)	105 (96%)	0.481
No success	4 (2%)	4 (4%)	0.480

*_P_-value of Fischer's exact and x^2 tests in categorical variables and t-test in continuous variables; DCB - drug-coated balloon

Table 4. Occurrence of MACE

	All n=286	15 mm n=177	20 mm n=109	*P*-value
MACE during hospital course	6 (2.1 %)	3 (1.7%)	3 (2.8%)	0.554
Death	1 (0.3%)	1 (0.6%)	0 (0.0%)	0.427
Myocardial infarction	2 (0.7%)	1 (0.6%)	1 (0.9%)	0.931
TLR	3 (1.1%)	2 (1.1%)	1 (0.9%)	0.341
MACE at 2-year follow-up	71 (24.8%)	41 (23.2%)	30 (27.5%)	0.408
Death	1 (0.3%)	0 (0.0%)	1 (0.9%)	0.203
Myocardial infarction	25 (8.7%)	13 (7.3%)	14 (12.8%)	0.294
TLR	62 (21.7%)	38 (21.4%)	24 (22.0%)	0.925

*_P_-value of x^2 test in categorical variables; MACE - major adverse cardiac events; TLR - target lesion revascularization

results) is recommended in ISR (8). DCB angioplasty is particularly very promising in ISR as no additional stent layer is needed. In a previous analysis, we demonstrated that Pantera Lux DCBs were superior to Sequent Please DCBs in prevention of adverse events (15). A tendency towards a higher incidence of MACE in patients treated with longer DCBs was observed. Therefore, we aimed to systematically investigate this issue in the present analysis. Contrary to our initial expectation, the present study suggests that DCB length does not impact the clinical outcome. Although patients undergoing treatment using 20-mm DCB might have had longer lesions, their outcome was not impaired. Hypothetically, a higher release of paclitaxel could counterbalance the more extensive stage of coronary artery disease represented by longer lesions.

However, this pilot study had several limitations. The number of patients in this pilot analysis was limited. It was a non-randomized, single-center analysis; however, it reflected a real-world population. Moreover, due to the retrospective design of this analysis, procedural data are limited; especially, QCA was not routinely conducted. Although QCA is a known standard procedure, there is also some evidence for an inter-core lab variability, especially concerning bifurcation stenosis (16). Moreover, it has been shown that evaluation of lesions using QCA is not superior to assessment by the interventional cardiologist (17). Therefore, lesion length is estimated regarding the pre-dilatation parameters by the interventionalist at our center. Furthermore, several patients presented with initial stent implantation which was conducted in external

hospitals; thus, information about stent length was not available for every case. Consequently, standard ratios like stent to balloon length ratio and lesion to balloon length ratio are missing in this study. Additionally, no intravascular ultrasound or optical coherence tomography was performed. Therefore, we were unable to evaluate angiographic mismatch. Despite these important limitations regarding procedural details, the aim of this pilot study was to focus on the evaluation of DCB length as predictor of clinical outcome. We concluded that DCB length was not associated with clinical outcome.

The results of this study might lead to the hypothesis that a moderate oversizing of DCB does not affect long-term clinical outcome. However, despite the fact that there were no significant differences in clinical outcome, MACE were numerically higher in 20-mm DCB-treated patients. Additionally, 15-mm DCBs were more frequently used in bifurcation stenosis cases. Besides that, patients' characteristics, prior disease, clinical presentation, and procedural details did not significantly differ between the groups. However, even non-significant differences might have biased the results. The number of patients was too small to allow reasonable multivariate analyses. In this rapidly evolving field owing to advanced technology, the findings of our study have to be confirmed in large-scale, randomized clinical trials and meta-analyses.

Conclusion

DCB length was not associated with clinical outcome. Rates of MACE did not differ between the 15-mm and 20-mm DCB-treated patients during hospital stay and 2-year follow-up. These findings have to be reconfirmed in clinical trials and meta-analyses.

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