

Percutaneous Coronary Intervention using a Full Metal Jacket with Drug-eluting Stents: Major Adverse Cardiac Events at One Year

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Abstract

Background: The clinical benefit of percutaneous coronary intervention (PCI) for long coronary lesions is unclear; furthermore, concerns have been raised about its safety.

Objectives: To evaluate the predictors of major adverse cardiac events (MACE) associated with PCI using a full metal jacket (FMJ), defined as overlapping drug-eluting stents (DES) measuring >60 mm in length, for very long lesions.

Methods: We enrolled 136 consecutive patients with long coronary lesions requiring FMJ in our single-center registry. The primary endpoint included the combined occurrence of all-cause death, myocardial infarction (MI), and target vessel revascularization (TVR). Demographic, clinical, angiographic, and procedural variables were evaluated using stepwise Cox regression analysis to determine independent predictors of outcome.

Results: The mean length of stent per lesion was 73.2 ± 12.3 mm and the mean reference vessel diameter was 2.9 ± 0.6 mm. Angiographic success was 96.3%. Freedom from MACE was 94.9% at 30 days and 85.3% at one year. At the one-year follow-up, the all-cause mortality rate was 3.7% (1.5% cardiac deaths), the MI rate was 3.7%, and the incidence of definite or probable stent thrombosis (ST) was 2.9%. Female gender [hazard ratio (HR), 4.40; 95% confidence interval (CI), 1.81–10.66; $p = 0.001$] and non-right coronary artery PCI (HR, 3.49; 95%CI, 1.42–8.59; $p = 0.006$) were independent predictors of MACE at one year. Freedom from adverse events at one year was higher in patients with stable angina who underwent PCI (HR, 0.33; 95%CI, 0.13–0.80; $p = 0.014$).

Conclusions: PCI using FMJ with DES for very long lesions was efficacious but associated with a high rate of ST at the one-year follow-up. However, the rate of cardiac mortality, nonprocedure-related MI, and MACE was relatively low. Target coronary vessel PCI, clinical presentation, and female gender are new contemporary clinical factors that appear to have adverse effects on the outcome of PCI using FMJ for long lesions. (Arq Bras Cardiol. 2013;101(2):117-126)

Keywords: Percutaneous Coronary Intervention; Drug-Eluting Stents; Coronary Artery Disease / therapy; Coronary angioplasty for long lesions.

Introduction

Multiple overlapping coronary stents are used for the treatment of long lesions or tandem lesions. Recently, the stent length has been increased for full lesion coverage. In the bare metal stent era, a longer stented segment resulted in a higher risk of restenosis and was thus avoided¹. Drug-eluting stents (DES) subsequently proved to decrease the need for reintervention; consequently, they replaced bare metal stents (BMS) in percutaneous coronary intervention (PCI) for complex long lesions². A few small registries have suggested that PCI using a full metal jacket (FMJ) with DES may be a

safe procedure for the treatment of diffuse coronary lesions, with acceptable immediate and late clinical outcomes³⁻⁶. Other factors related to vessel diameter and lesion location are also reported to impact the rate of restenosis, including the use of vein grafts and the presence of ostial lesions and bifurcations⁷. The clinical effects of very long and overlapping DES implantation in different clinical and angiographic settings remain unknown; furthermore, the risk of stent thrombosis (ST) has raised concerns. This study was performed to evaluate the predictors of long-term major adverse cardiac events (MACE) associated with PCI using FMJ, defined as overlapping DES measuring ≥ 60 mm in length, for very long lesions.

Methods

Patient population

From a dedicated database of 5158 consecutive PCI procedures performed between 2003 and 2007 at a high-volume coronary intervention laboratory, we

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retrospectively identified 136 patients (2.6%) who underwent PCI with multiple overlapping DES measuring ≥ 60 mm in length (FMJ) for diffuse long lesions or tandem lesions and extensive dissections. Patients were considered eligible if they were >18 years of age and had clinical evidence of myocardial ischemia.

Written informed consent was obtained from all patients who were part of the prospective database.

Stenting procedure

All PCI interventions were performed using standard techniques. The choice of treatment strategy, DES selection (paclitaxel-, sirolimus-, zotarolimus-, or everolimus-eluting stents), the use of glycoprotein IIb/IIIa inhibitors, and the need for post-dilatation were left to the operator's discretion. Some degree of overlap between stents was considered as qualifying criteria. Angiographic success was defined as the presence of $<30\%$ residual stenosis.

In-stent restenosis (ISR) was defined as the presence of a stenotic lesion occupying $>50\%$ of the vessel diameter in a previous stented segment. Chronic total occlusion (CTO) was defined as an artery occluded for more than three months, with thrombolysis in myocardial infarction grade 0 flow at the start of the procedure. A bifurcation was defined if the overlapping stents covered a side branch visually estimated to be >2 mm in diameter by the operator.

All patients were pre-treated with clopidogrel (75 mg if already in chronic therapy with clopidogrel for >10 days, and 300 or 600 mg if not). After PCI, the patients were prescribed indefinite aspirin (100 mg/day) therapy and clopidogrel (75 mg/day) therapy for minimum^{6–12} months.

Quantitative coronary angiography (QCA)

Angiographic measurements were made during diastole using a guiding catheter to calibrate magnification. A quantitative angiographic analysis system (Siemens®) was used to obtain, record, and analyze baseline coronary angiograms using the single projection showing the most severe stenosis. The percentage of diameter stenosis, minimal lumen diameter, and reference vessel diameter were measured before dilatation and after the stenting procedure.

Endpoint definition and clinical follow-up

As a primary endpoint, we assessed the incidence of MACE, defined as a composite of all-cause death, MI, and target vessel revascularization (TVR) at one year. MACE at 30 days was used to assess the acute safety of the procedure.

Deaths were classified as cardiac or noncardiac, with all deaths considered cardiac unless an unequivocal noncardiac cause could be established. MI was diagnosed when there were ischemic symptoms or new electrocardiographic changes accompanied by a typical rise and gradual fall (for troponin I) or a more rapid rise and fall (for CK-MB) in the levels of biochemical markers for myocardial necrosis. Periprocedural MI was defined as an increase in troponin or CK-MB levels to more than three times the upper reference limit in the first 48 h after PCI⁸. Repeat target

lesion revascularization (TLR) included repeat percutaneous or surgical intervention in the previously treated segment, including the region of the implanted stent and a region 5 mm proximal or distal to the edge of the stent. TVR was defined as repeat PCI or coronary artery bypass grafting (CABG) of the target vessel. Target vessel failure was defined as cardiac death, MI, or TLR that was not attributable to a vessel other than the target vessel.

Definite or probable ST was defined according to the Academic Research and Consortium (ARC) definition⁹.

Clinical follow-up of all patients was conducted via telephone using a pre-specified interview; in addition, clinical hospital records were reviewed for patients who were re-admitted.

Statistical analyses

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov's test and for equality of variances using the Levene's test. Continuous variables are reported as means \pm standard deviations (SDs) and were compared using an independent sample Student's *t*-test. The Mann–Whitney U test was used to compare groups when variables did not display a normal distribution or equality of variances. Categorical variables are reported as percentages and were compared using the Chi-square test or Fisher exact test as appropriate.

Univariate logistic regression analysis was used to calculate the hazard ratio (HR) for the occurrence of MACE at one year. In addition, to determine independent predictors of the primary endpoint, we performed multiple logistic regression analysis after adjusting for significant demographic, angiographic, and procedural characteristics. The independent variables for entry into the multivariate model were selected according to their significance in univariate testing [$p < 0.1$ and shorter 95% confidence intervals (CI)]. The final model was built by forward stepwise variable selection with entry and exit criteria at the $p = 0.05$ and $p = 0.1$ levels, respectively. The cumulative incidence of adverse events was calculated according to the Kaplan–Meier method and differences were assessed using the log-rank test. All tests were two-sided. A *p* value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics for Windows, version 17.0 (SAS Institute, Cary, NC, USA).

Results

Baseline clinical characteristics

Baseline clinical and procedural characteristics are presented in Tables 1 and 2. The mean patient age was 62 ± 10 years, and the proportion of females and patients with diabetes mellitus was 26% and 38%, respectively. The index procedure was performed in the setting of acute coronary syndrome for 35% patients (unstable angina, $n = 9$; MI with non-ST segment elevation, $n = 19$; MI with ST segment elevation, $n = 20$). A total of 23 patients (17%) had left ventricular dysfunction (ejection fraction, $<50\%$)

Table 1 - Baseline clinical characteristics and their relation to major adverse clinical events at the 30-day and one-year follow-up as per univariate analysis

Baseline clinical variables	MACE 30-days			p value	MACE 1-year		p value
	Total Population (n = 136)	Yes (n = 7)	No (n = 129)		Yes (n = 20)	No (n = 116)	
Demographics							
Age (years)	62 ± 10	70 ± 4	62 ± 10	0,025	66 ± 10	62 ± 10	0,058
Age >75 years, n (%)	16 (12)	1 (14)	15 (12)	0,592	4 (20)	12 (10)	0,255
Female sex, n (%)	35 (26)	4 (57)	31 (24)	0,072	11 (55)	24 (21)	0,002
CV risk factors, n (%)							
Diabetes Mellitus	51 (38)	2 (29)	49 (38)	0,711	6 (30)	45 (39)	0,618
Dyslipidemia	82 (60)	4 (57)	78 (61)	1,000	13 (65)	69 (60)	0,806
Smoking habits	33 (24)	1 (14)	32 (25)	1,000	3 (15)	30 (26)	0,402
Hypertension	91 (67)	3 (43)	88 (68)	0,219	13 (65)	78 (67)	1,000
Prior CV history, n (%)							
Previous MI	40 (29)	2 (29)	38 (30)	1,000	6 (30)	34 (29)	1,000
Previous PCI	53 (39)	4 (57)	49 (38)	0,431	8 (40)	45 (39)	1,000
Previous CABG	27 (20)	1 (14)	26 (20)	1,000	6 (30)	21 (18)	0,231
Stroke	4 (3)	0 (0)	4 (3)	1,000	0 (0)	4 (3)	1,000
Peripheral artery disease	8 (6)	1 (14)	7 (5)	0,352	1 (5)	7 (6)	1,000
Indication for PCI, n (%)							
Stable coronary artery disease	88 (65)	0 (0)	88 (68)	0,001	8 (40)	80 (69)	0,021
Acute coronary syndrome	48 (35)	7 (100)	41 (32)	0,001	12 (60)	36 (31)	0,021
Unstable angina	9 (7)	1 (14)	8 (6)	0,388	2 (10)	7 (6)	0,620
MI with non-ST segment -elevation	19 (14)	1 (14)	18 (14)	1,000	5 (25)	14 (12)	0,158
MI with ST segment elevation	20 (15)	5 (71)	15 (12)	0,001	5 (25)	15 (13)	0,175
Multivessel coronary disease	96 (71)	5 (71)	91 (71)	1,000	15 (75)	81 (70)	0,793
Left ventricular ejection fraction < 50%	23 (17)	3 (43)	20 (16)	0,094	5 (25)	18 (16)	0,333

MACE: major adverse cardiac events; CV: cardiovascular; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.

and 71% had multivessel disease. Several patients had a history of clinically overt cardiovascular disease, including prior MI (29%), and many had undergone previous coronary revascularization with PCI (39%) or CABG (20%).

Procedural characteristics

PCI was performed for the left anterior descending (LAD) in 23% patients, the left circumflex (LCX) artery in 8%, the right coronary artery (RCA) in 65%, and a vein bypass graft in 4%. PCI was performed for ISR in 39% patients, CTO in 26%, and a major bifurcation in 6%. Only 4% patients were treated for dissection (n = 6). Sirolimus- or paclitaxel-eluting stents were used for 112 patients (82%) while second-generation zotarolimus- or everolimus-eluting stents were used for the remaining 24 (18%). Glycoprotein IIb/IIIa inhibitors were administered during 54% procedures. The mean length of stent per lesion was 73 ± 12 mm (range, 60–114 mm) and the median stent diameter was 2.5 mm. The median number of stent overlaps per lesion was three (range, 2–6).

Angiographic success was 96%. Among the five patients with final angiographic diameter stenosis >30%, two experienced ST (one acute and one late).

Cardiovascular events at the 30-day follow-up

At the one-month follow-up, three patients (2.2%) had died (one from cardiovascular causes), two (1.5%) had suffered non-procedure related MI, and four (2.9%) had undergone TVR, resulting in a combined MACE incidence of 5.1% (Table 3). The prevalence of periprocedural MI was 5.1%.

According to univariate analysis, the predictors of MACE at 30 days were acute coronary syndrome, mainly MI with ST segment elevation at the index procedure (HR, 15.64; 95%CI, 3.03–80.70; p = 0.001), LAD PCI (HR, 8.84; 95%CI, 1.71–45.55; p = 0.009), age (HR, 1.09; 95%CI, 1.00–1.18; p = 0.050), and the use of second-generation stents (HR, 6.50; 95%CI, 1.45–29.04; p = 0.014). RCA PCI (HR, 0.09; 95%CI, 0.01–0.73; p = 0.024) was associated with a more favourable outcome (Tables 1 and 2).

Table 2 - Angiographic and procedural characteristics in relation to occurrence of major adverse cardiac events (MACE) at the 30-day and one-year follow-up as per univariate analysis

Angiographic and procedural characteristics	MACE 30 days			p value	MACE 1 year		p value
	Total Population (n = 136)	Yes (n = 7)	No (n = 129)		Yes (n = 20)	No (n = 116)	
Lesion characteristics, n (%)							
Target coronary vessel							
Left anterior descending artery	31 (23)	5 (71)	26 (20)	0,007	7 (35)	24 (21)	0,162
Left circumflex artery	11 (8)	0 (0)	11 (9)	1,000	1 (5)	10 (9)	1,000
Right coronary artery	88 (65)	1 (14)	87 (67)	0,008	8 (40)	80 (69)	0,021
Vein graft	6 (4)	1 (14)	5 (4)	0,276	4 (20)	2 (2)	0,004
Chronic total occlusion	35 (26)	0 (0)	35 (27)	0,339	2 (11)	33 (29)	0,156
Ostial lesion	11 (8)	0 (0)	11 (9)	1,000	0 (0)	11 (10)	0,363
Bifurcation	8 (6)	0 (0)	8 (6)	1,000	0 (0)	8 (7)	0,600
Dissection	6 (4)	0 (0)	6 (5)	1,000	1 (5)	5 (4)	1,000
In-stent reestenosis	53 (39)	4 (57)	49 (38)	0,431	8 (40)	45 (39)	1,000
Procedural characteristics							
No stents per lesion, n (%)	3,0 ± 0,8	3,1 ± 0,4	3,0 ± 0,8	0,575	2,8 ± 0,5	3,0 ± 0,8	0,239
Stented length (mm)	73,2 ± 12,3	69,7 ± 10,7	73,4 ± 12,4	0,445	68,1 ± 10,4	74,1 ± 12,4	0,027
Minimal stent diameter (mm)	2,6 ± 0,4	2,8 ± 0,6	2,6 ± 0,3	0,233	2,7 ± 0,5	2,6 ± 0,3	0,199
Use of second generation stents, n (%)	24 (18)	4 (57)	20 (16)	0,019	5 (25)	19 (16)	0,350
Glycoprotein IIb/IIIa inhibitor, n (%)	73 (54)	6 (86)	67 (52)	0,122	14 (70)	59 (51)	0,147
Post-dilatation, n (%)	71 (52)	3 (43)	68 (53)	0,258	7 (35)	64 (55)	0,820
Quantitative coronary angiography							
Lesion length (mm)	58,9 ± 19,5	41,7 ± 16,4	59,6 ± 19,4	0,120	49,6 ± 17,0	60,5 ± 19,6	0,086
Reference vessel diameter (mm)	2,9 ± 0,6	3,2 ± 0,7	2,9 ± 0,6	0,235	3,1 ± 0,6	2,9 ± 0,6	0,145
Before intervention							
Minimal lumen diameter (mm)	0,3 ± 0,4	0,5 ± 0,5	0,3 ± 0,4	0,503	0,4 ± 0,5	0,3 ± 0,4	0,693
Diameter stenosis (%)	88,4 ± 14,1	85,0 ± 16,5	88,6 ± 14,0	0,545	87,3 ± 15,8	88,6 ± 13,8	0,701
After intervention							
Minimal lumen diameter (mm)	2,4 ± 0,4	2,6 ± 0,5	2,4 ± 0,4	0,301	2,4 ± 0,4	2,4 ± 0,4	0,969
Diameter stenosis (%)	20,0 ± 7,1	20,7 ± 6,4	20,0 ± 7,2	0,816	20,9 ± 7,4	19,8 ± 7,1	0,558

Table 3 - Major adverse cardiac events (MACE) at the 30-day and one-year follow-up

Major clinical events at the 30-day and one-year follow-up, n (%)	30 days	one year
All-cause death	3 (2,2)	5 (3,7)
Cardiac death	1 (0,7)	2 (1,5)
Myocardial infarction	2 (1,5)	5 (3,7)
Target lesion revascularization	1 (0,7)	10 (7,4)
Target vessel revascularization	4 (2,9)	13 (9,6)
Target vessel failure	4 (2,9)	15 (11,0)
MACE	7 (5,1)	20 (14,7)
Definite or probable stent thrombosis (ARC definition)	2 (1,5)	4 (2,9)

MACE at the one-year follow-up

Follow-up at one year was available for all patients (mean, 31 ± 18 months). At the one-year follow-up, five patients (3.7%) had died (two from cardiovascular causes), five (3.7%) had suffered MI, and 13 (9.6%) had undergone TVR, resulting in a combined MACE incidence of 14.7% (Table 3).

According to univariate analysis, RCA PCI appeared to be a protective factor against long-term adverse clinical events. Univariate analysis revealed female gender, acute coronary syndrome at the index procedure, and bypass graft PCI as predictors of MACE at one year. In our study, PCI for CTO and PCI for ISR were not associated with MACE as per univariate analysis (CTO- vs. non-CTO-related MACE rate, 6% vs. 17%; $p = 0.16$; ISR- vs. non-ISR-related MACE rate, 15% vs. 15%; $p = 0.92$). The presence of diabetes, the use of first-generation DES, stent length, and reference vessel diameter were not found to be predictors of adverse events at the one-year follow-up in our study (Tables 1 and 2).

After multivariate adjustment, the only independent predictors of MACE at one year were female gender and non-RCA PCI. PCI in the setting of acute coronary syndrome at the index procedure and PCI of saphenous vein grafts were not predictors of MACE at one year according to multivariate analysis (Table 4).

Target vessel revascularization at the one-year follow-up

The incidence of TVR was 9.6% at the end of one year. As per univariate analysis, RCA PCI was the only predictor of a favorable outcome. Multivariate Cox regression analysis also revealed RCA PCI to be an independent predictor of a favorable outcome. In addition, female gender was an independent predictor of TVR at one year (Table 5).

ST

During the one-year follow-up period, four patients (2.9%) suffered at least one ST, with two being acute and two being late ST. As per the ARC definition, three patients had definite ST and one had probable ST. The treated vessel was the RCA in two patients, the LAD in one, and a bypass graft in one. ST occurred after MI as the index PCI indication (0 and 343 days after the index procedure) in three patients and in the setting of stable coronary artery disease in one (64 days after PCI). All STs occurred while the patients were still receiving dual antiplatelet therapy. All four patients were alive at the one-year follow-up.

Subset analysis

Vein graft

PCI for a vein bypass graft was performed in only six patients in our study; however, the rate of MACE at the one-year follow-up was higher (67%) with this procedure than with PCI in native coronary vessels (12%, $p = 0.004$; Figure 1A).

Native coronary vessels

LAD PCI affected clinical outcomes negatively, with a clear separation of event-free survival curves during the acute phase after PCI (16% patients experienced MACE at 30 days). This separation was maintained throughout follow-up (23% MACE at one year; Figure 1A). Among these patients, 71% had multivessel disease and 42% had acute coronary syndrome.

Clinical presentation

With regard to clinical presentation at the index procedure, the rate of MACE (25% vs. 9%, $p = 0.02$), all-cause mortality (10% vs. 0%, $p = 0.01$) and nonfatal MI (8% vs. 1% of non-fatal MI, $p = 0.05$) at the one-year follow-up was higher for patients with acute coronary syndrome than for patients with stable coronary disease (Figure 1B).

Gender

Finally, we found that the female gender was associated with a higher restenosis rate at the one-year follow-up compared with the male gender (17% vs. 4%; $p = 0.02$). However, there was no difference in the rate of death or MI between men and women. Compared with men, women who underwent PCI in our study were older (>75 years of age, 26% vs. 7%, $p = 0.01$) and slightly more likely to be diabetic (49% vs. 34%, $p = 0.16$). In addition, women exhibited a higher incidence of acute coronary syndrome at the index procedure compared with men (54% vs. 29%, $p = 0.01$; Figure 1C).

Discussion

Previous studies reported that the treatment of long segments with BMS was associated with a higher risk of restenosis and should be avoided¹. Once DES were proved effective in decreasing ISR and the need for reintervention¹⁰, they began to replace BMS in PCI, mostly for complex lesions at high risk of restenosis¹¹, such as long lesions¹. However, despite being effective in decreasing ISR and TVR, DES were associated with a high risk of ST, mostly late ST¹². Stent length was initially perceived as a predictor of ST due to more frequent incomplete contact with the vessel wall¹² and the increased risk of late stent malapposition that was usually caused by positive remodelling or suboptimal stent implantation¹³, although polymer-associated thrombogenicity and delayed vascular healing could also play a role¹⁴. A few small registries suggested that PCI using FMJ with DES may be safe for the treatment of diffuse coronary lesions, with acceptable immediate and late clinical outcomes³⁻⁶.

In our study, patients that underwent PCI using FMJ with DES exhibited a low rate of MACE (14.7%) at the one-year follow-up, with one-year cardiac death rate of 1.5%, MI rate of 3.7%, and TVR rate of 9.6% in the same period of time. These results are in agreement with other published results^{3,6}.

Table 4 - Independent predictors of major adverse cardiac events (MACE) at the one-year follow-up

MACE 1 year Variable	Univariate			Multivariate		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Female sex	3,92	1,62-9,46	0,002	4,40	1,81-10,66	0,001
Right coronary artery PCI	0,33	0,13-0,80	0,014	0,29	0,12-0,70	0,006
Acute coronary syndrome	3,07	1,25-7,50	0,014	1,96	0,73-5,25	0,067
Bypass graft PCI	6,11	2,04-18,31	0,001	2,12	0,58-7,79	0,123
Stented length	0,95	0,91-1,00	0,054	0,97	0,93-1,02	0,225
Age	1,04	1,00-1,09	0,061	1,02	0,97-1,06	0,311
Use of 2 nd generation stents	1,74	0,63-4,79	0,284			
LVEF < 50%	1,78	0,65-4,89	0,265			
Diabetes	0,69	0,27-1,81	0,456			
Lesion length	0,97	0,94-1,00	0,082			
Reference vessel diameter	1,88	0,82-4,31	0,134			

PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction.

Table 5 - Independent predictors of target vessel revascularization at the one-year follow-up

TVR 1 year Variable	Univariate			Multivariate		
	Hazard ratio	95% CI	p value	Hazard ratio	95% CI	p value
Female sex	2,64	0,89-7,86	0,081	3,03	1,01-9,09	0,047
Right coronary artery PCI	0,30	0,10-0,92	0,035	0,27	0,09-0,83	0,023
Stented length	0,95	0,88-1,00	0,070	0,95	0,89-1,02	0,161
Acute coronary syndrome	1,72	0,58-5,12	0,330			
Use of 2 nd generation stents	1,51	0,42-5,50	0,529			
LVEF < 50%	1,53	0,42-5,55	0,521			
Diabetes	0,70	0,27-1,81	0,459			
Lesion length	0,97	0,94-1,01	0,176			
Reference artery diameter	1,55	0,55-4,42	0,408			

TVR: target vessel revascularization; PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction.

A frequent condition associated with the use of multiple overlapping stents for diffuse coronary disease is the high incidence of periprocedural MI, although its significance remains unknown. In our study, the prevalence of periprocedural MI was 5.1%, which was lower than that reported by Lee et al⁴ (19.6%) and Sharp et al⁶ (9.5% for single-vessel procedures and 19.0% for multivessel procedures) and higher than that reported by Aoki et al³ (4.0%). However, the low one-year cardiac mortality and nonprocedure-related MI rates in our cohort with complex lesions was a positive outcome.

The TLR rate at the one-year follow-up in our study was lower (7.4%) than that reported by Sharp et al⁶. Angiographic follow-up was not performed in our study, which may be a possible cause for this difference. In the era of BMS, the treatment of diffuse coronary lesions often relied on bypass surgery because of the high risk

of re-stenosis associated with PCI using extremely long stents¹⁵. The rate of repeat revascularization (23.4%) and MACE (27%) at the one-year follow-up was higher in the ADVANCE¹⁶ and TULIP¹⁷ trials, where in long lesions were treated with BMS, than in our study. DES have thus been proven to decrease the need for repeat revascularization.

In the current study, the overall rate of ST (definite/probable) was 2.9% at the one-year follow-up, similar to the findings from the largest study of FMJ published till date⁶, which reported a 1.1% and 2.0% cumulative incidence of ST at 30 days and one year, respectively. According to data pooled from eight trials on sirolimus- and paclitaxel-eluting stents¹⁸, ST occurred less frequently (0.5% for both stents at 30 days and 0.6% and 0.9% for sirolimus- and paclitaxel-eluting stents, respectively, at one year). However, the cumulative incidence of ST in nonrandomized registry patients was always higher because

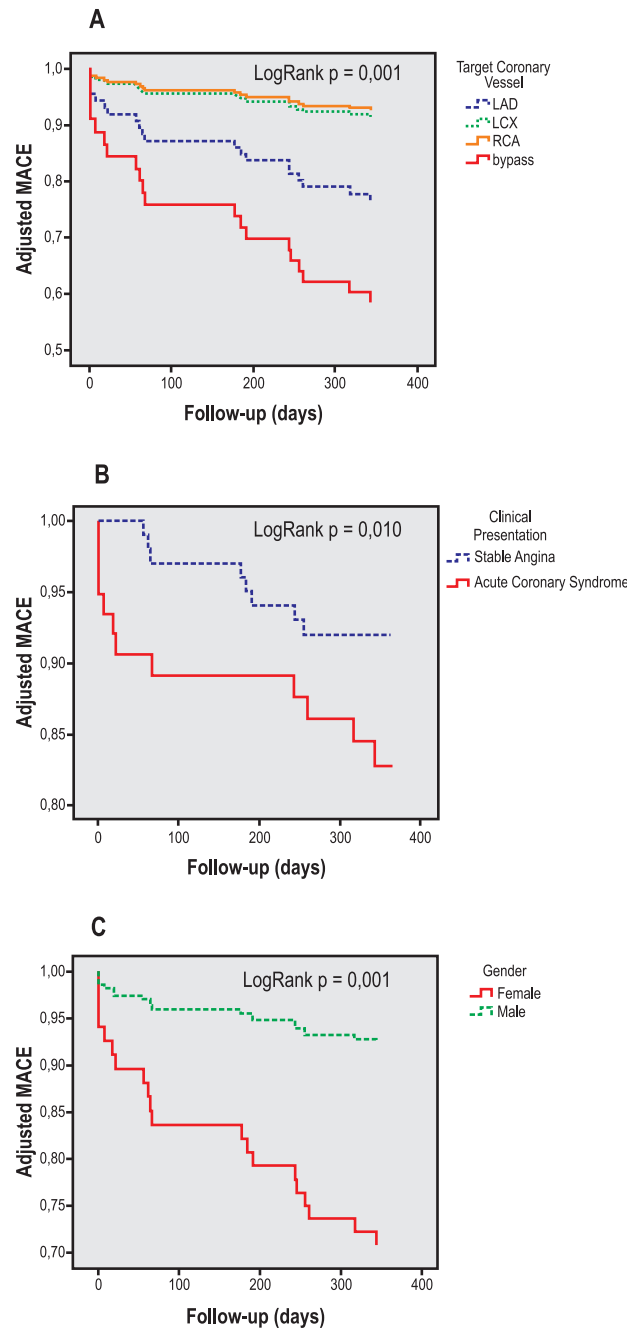


Figure 1 - Event-free survival curves for major adverse cardiac events (MACE) stratified by target coronary vessel (A), clinical presentation at index procedure (B), and gender (C). LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery.

the results of PCI expanded to more complex lesions and patients¹⁹. The clinical consequence of ST in our study was nonfatal MI in all patients.

Several studies on BMS showed that a longer stented segment^{20,21}, a small reference vessel diameter²⁰, and the presence of diabetes^{22,23} were independent predictors of restenosis. However, stent length, vessel diameter, and the

presence of diabetes were not predictive of TVR in our study. This lack of effect of total stent length is in accordance with the finding from previous studies on FMJ procedures³⁻⁶. The fact that stent length no longer predicts restenosis after PCI using DES may be one possible explanation; however, further studies are required to clarify this. Increasing stent length to optimize lesion coverage and avoid geographical

overlooks may contribute to the decrease in the restenosis rate in some cases. Moreover, we found that the number of stents was also not predictive of late clinical outcome or TVR, similar to the findings from the study by Kornowsky et al¹⁵. This suggests that this strategy to treat diffuse long lesions is feasible. The fact that TVR was not predicted by vessel diameter and the presence of diabetes has been controversial, with a disparity among results in previous studies^{4,6}. It is important to note that the results of the present study were obtained for relatively large vessels with an average diameter of 2.9 mm.

In our study, there was no difference in the rate of adverse clinical events at the one-year follow-up between patients treated with first-generation stents and those treated with second-generation stents. These results are in agreement with those of other studies^{24,25}, suggesting that both DES designs can be equally effective for the treatment of these complex lesions.

We found that anatomic location, clinical presentation at index procedure, and gender played an important role in achieving favourable outcomes of treatment with multiple overlapping stents for diffuse coronary lesions.

In this registry, FMJ with DES was implanted more often in the RCA, and this PCI procedure appeared to be associated with lower acute and long-term adverse clinical events. Although FMJ was placed in vein grafts in only 4% patients in our study, the procedure was associated with a higher rate of MACE at the one-year follow-up (67% in patients with treated vein grafts vs. 12% in patients with treated native coronary vessels). This finding is in line with those of previous studies that showed a higher restenosis rate in vein bypass grafts than in native coronary arteries²⁶. A recent meta-analysis suggested that DES is associated with a lower need for reintervention and a lower mortality rate compared with BMS in patients who undergo PCI for vein bypass grafts²⁷. However, DES does not show long-term advantages in these patients²⁸. The sample of patients who received FMJ in vein grafts in our study was too small, thus limiting our ability to draw definite conclusions in this regard.

With regard to the use of multiple overlapping DES for the treatment of diffuse disease in the LAD, there is only one published study that has reported good midterm clinical outcomes; however, the incidence of restenosis was 19.6% in that study²⁹. In our study, the use of FMJ in the LAD negatively affected clinical outcomes. The presence of diffuse disease in the LAD is normally a contraindication for CABG and is usually associated with a higher atherosclerosis coronary burden; this can partially explain the poor outcomes in this patient group in our study.

Our data suggests that FMJ used in the setting of acute coronary syndrome is associated with higher rates of MACE, thus raising safety concerns. These findings are in agreement with those of previous studies where the risk of MACE was higher in patients with acute coronary disease than in those with chronic stable disease^{30,31}. A possible reason may be the increased propensity for acute thrombotic complications after PCI.

We also found that women showed higher restenosis rates at the one-year follow-up compared with men, although there were no gender differences in the rate of death or MI. Compared with men, women in our study were older, more likely to be diabetic, and had a higher incidence of acute coronary syndrome at the index procedure. Previous studies that reported increased rates of adverse events in women who underwent PCI for complex lesions also showed that women had worse baseline characteristics³².

Despite the newly identified variables, additional data is required to determine the worst clinical scenarios where PCI using multiple overlapping DES for diffuse coronary lesions should be avoided. Large-scale multicenter registries are necessary to reliably determine the clinical outcomes of PCI using FMJ with DES for diffuse coronary lesions and assess the risk of ST, death, and MI.

Study limitations

This study has several limitations. First, this was a retrospective evaluation of a small cohort of patients from a single institution. The small number of patients can be partly explained by the low incidence rate of these complex lesions in the general population and the fact that surgical revascularization is the most commonly selected method to treat patients with long lesions, particularly those in the LAD. The small number of events limits our ability to rule out other potential predictors of events. Second, this was a nonrandomized clinical trial lacking a control group. Third, the choice of DES was left to the operator, leading to possible selection bias as restenosis rates in lesions with different types of stents may vary.

Conclusion

PCI using FMJ with DES for diffuse coronary lesions was efficacious but associated with a high rate of ST at the one-year follow-up. However, the rate of cardiac mortality, nonprocedure-related MI, and MACE was relatively low with this procedure. Target coronary vessel PCI (non-RCA), clinical presentation (acute coronary syndromes), and female gender are new contemporary clinical factors that appear to have adverse effects on the outcome of PCI using FMJ for long lesions.

Author contributions

Conception and design of the research: Teles RC; Acquisition of data: Cale R, Rosário I, Sousa P, Brito J; Analysis and interpretation of the data: Cale R, Almeida M; Statistical analysis: Cale R; Writing of the manuscript: Cale R; Critical revision of the manuscript for intellectual content: Teles RC, Almeida M, Raposo L, Gonçalves P, Gabriel H, Mendes M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References

1. Kobayashi Y, De Gregorio J, Kobayashi N, Akiyama T, Reimers B, Finci L, et al. Stented segment length as an independent predictor of restenosis. *J Am Coll Cardiol*. 1999;34(3):651-9.
2. Dawkins KD, Grube E, Guagliumi G, Banning AP, Zmudka K, Colombo A, et al; TAXUS VI Investigators. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation*. 2005;112(21):3306-13.
3. Aoki J, Ong AT, Rodriguez Granillo GA, McFadden EP, van Mieghem CA, Valgimigli M, et al. "Full metal jacket" (stented length \geq 64 mm) using drug-eluting stents for de novo coronary artery lesions. *Am Heart J*. 2005;150(5):994-9.
4. Lee CW, Park KH, Kim YH, Hong MK, Kim JJ, Park SW, et al. Clinical and angiographic outcomes after placement of multiple overlapping drug-eluting stents in diffuse coronary lesions. *Am J Cardiol*. 2006;98(7):918-22.
5. Andron M, Ramsdale DR, Rao A, Ramsdale KA, Albouaini K. Clinical outcomes after percutaneous coronary intervention involving very long segments of drug-eluting stent implantation: single-center experience. *J Invasive Cardiol*. 2009;21(2):46-50.
6. Sharp AS, Latib A, Ielasi A, Larosa C, Godino C, Saolini M, et al. Long-term follow-up on a large cohort of "full-metal jacket" percutaneous coronary intervention procedures. *Circ Cardiovasc Interv*. 2009;2(5):416-22.
7. Hoffmann R, Mintz GS. Coronary in-stent restenosis – predictors, treatment and prevention. *Eur Heart J*. 2000;21(21):1739-49.
8. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;27(22):2173-95.
9. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Academic Research Consortium. Clinical end-points in coronary stent trials—a case for standardized definitions. *Circulation*. 2007;115(17):2344-51.
10. Morice M, Serruys P, Sousa JE, Fajadet J, Hayashi EB, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346(23):1773-80.
11. Stone GW, Ellis SG, Cannon L, Mann JT, Greenberg JD, Spriggs D, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA*. 2005;294(10):1215-23.
12. Moreno R, Fernández C, Hernández R, Alfonso F, Angiolillo DJ, Sabaté M, et al. Drug-eluting stent thrombosis: results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol*. 2005;45(6):954-9.
13. van der Hoeven BL, Liem S, Dijkstra J, Bergheanu SC, Putter H., Antoni ML, et al. Stent malapposition after sirolimus-eluting and bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: acute and 9-month intravascular ultrasound results of the MISSION! intervention study. *JACC Cardiovasc Interv*. 2008;1(2):192-201.
14. Cook S, Ladich E, Nakazawa G, Eshthardi P, Neidhart M, Vogel R, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation*. 2009;120(5):391-9.
15. Kornowski R, Mehran R, Hong MK, Satler LF, Pichard AD, Kent KM, et al. Procedural results and late clinical outcomes after placement of three or more stents in single coronary lesions. *Circulation*. 1998;97(14):1355-61.
16. Serruys PW, Foley DP, Suttrop MJ, Rensing BJ, Suryapranata H, Materne P, et al. A randomized comparison of the value of additional stenting after optimal balloon angioplasty for long coronary lesions: final results of the additional value of NIR stents for the treatment of long coronary lesions (ADVANCE) study. *J Am Coll Cardiol*. 2002;39(3):393-9.
17. Oemrawsingh PV, Mintz GS, Schalij MJ, Zwinderman AH, Jukema JW, van der Wall EE et al; TULIP Study. Thrombocyte activity evaluation and effects of Ultrasound guidance in Long Intracoronary stent Placement. Intravascular ultrasound guidance improves angiographic and clinical outcome of stent implantation for long coronary artery stenosis: final results of a randomized comparison with angiographic guidance (TULIP study). *Circulation*. 2003;107(1):62-7.
18. Mauri L, Hsieh W, Massaro JM, Ho K, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356(10):1020-9.
19. Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293(17):2126-30.
20. Kobayashi Y, Gregorio J, Kobayashi N, Akiyama T, Reimers B, Finci L, et al. Stented segment length as an independent predictor of restenosis. *J Am Coll Cardiol*. 1999;34(3):651-9.
21. Foley DP, Pieper M, Wijns W, Suryapranata H, Grollier G, Legrand V, et al. The influence of stent length on clinical and angiographic outcome in patients undergoing elective stenting for native coronary artery lesions. *Eur Heart J*. 2001;22(17):1585-93.
22. Elezi S, Kastrati A, Pache J, Wehinger A, Hadamitzky M, Dirschinger J, et al. Diabetes mellitus and the clinical and angiographic outcome after coronary stent placement. *J Am Coll Cardiol*. 1998;32(7):1866-73.
23. Kastrati A, Schömig A, Elezi S, Schühlen H, Dirschinger J, Hadamitzky M, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol*. 1997;30(6):1428-36.
24. Park DW, Kim YH, Song HG, Ahn JM, Kim WJ, Lee JY, et al. Comparison of everolimus- and sirolimus-eluting stents in patients with long coronary artery lesions: a randomized LONG-DES-III (Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent III) Trial. *JACC Cardiovasc Interv*. 2011;4(10):1096-103.
25. Ahn JM, Park DW, Kim YH, Song H, Cho YR, Kim WJ, et al. Comparison of resolute zotarolimus-eluting stents and sirolimus-eluting stents in patients with de novo long coronary artery lesions: a randomized LONG-DES IV Trial. *Circ Cardiovasc Interv*. 2012;5(5):633-40.
26. de Feyter PJ, van Suylen RJ, de Jaegere PP, Topol EJ, Serruys PW. Balloon angioplasty for the treatment of lesions in saphenous vein bypass grafts. *J Am Coll Cardiol*. 1993;21(7):1539-49.
27. Sanchez-Recalde A, Jiménez Valero S, Moreno R, Barreales L, Lozano I, Galeote G, et al. Safety and efficacy of drug-eluting stents versus bare-metal stents in saphenous vein grafts lesions: a meta-analysis. *EuroIntervention*. 2010;6(1):149-60.
28. Brodie B, Wilson H, Stuckey T, Nussbaum M, Laurent S, Bradshaw B, et al; STENT Group. Outcomes with drug-eluting versus bare-metal stents in saphenous vein graft intervention: results from the STENT (Strategy transcatheter evaluation of new therapies) group. *JACC Cardiovasc Interv*. 2009;2(11):1105-12.
29. Tsagalou E, Chieffo A, Iakovou I, Ge L, Sangiorgi GM, Corvaja N, et al. Multiple overlapping drug-eluting stents to treat diffuse disease of the left anterior descending coronary artery. *J Am Coll Cardiol*. 2005;45(10):1570-3.
30. Hausleiter J, Kastrati A, Mehilli J, Schühlen H, Pache J, Dotzer F, et al. Predictive factors for early cardiac events and angiographic restenosis after coronary stent placement in small coronary arteries. *J Am Coll Cardiol*. 2002;40(5):882-9.
31. Schühlen H, Kastrati A, Dirschinger J, Hausleiter J, Elezi S, Wehinger A, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. *Circulation*. 1998;98(2):104-11.
32. Sheiban I, La Spina C, Cavallero E, Biondi-Zoccai G, Colombo F, Palmerini T, et al. Sex-related differences in patients undergoing percutaneous unprotected left main stenting. *EuroIntervention*. 2010;5(7):795-800.

