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CORONARY ARTERY DISEASE

Original Studies

Temporal Patterns of Drug-Eluting Stent Failure and Its Relationship With Clinical Outcomes

Cheol Whan Lee, MD, Jung-Min Ahn, MD, Sung-Han Yoon, MD, Jong-Young Lee, MD, Duk-Woo Park, MD, Soo-Jin Kang, MD, Seung-Whan Lee, MD, Young-Hak Kim, MD, Seong-Wook Park, MD, PhD, and Seung-Jung Park,* MD, PhD

Objectives: We investigated the temporal patterns of drug-eluting stents (DES) failure and its relationship with clinical outcomes in patients with DES failure. Background: Time to DES failure is widely variable, but little information is available on the temporal patterns of DES failure and its impact on clinical outcomes. Methods: The angiographic patterns of DES failure and clinical outcomes in 633 patients with 676 lesions who presented with their first instance of DES failure were analyzed. The primary outcome was all-cause death following treatment for DES failure. Results: DES failure occurred in a median of 10.1 months after the index procedure. We identified 548 and 85 instances of DES restenosis (86.6%) and stent thrombosis (13.4%), respectively. Patients were divided into three groups according to the interval from the index procedure to DES failure: group 1 (early DES failure: <12 months), group 2 (late: 12–36 months), and group 3 (very late: ≥36 months). Acute myocardial infarction was more common in patients who developed failure after ≥12 months than patients with earlier presentations. Focal DES failure was more common in group 1, whereas nonfocal DES failure in groups 2 and 3. During follow-up after retreatment (median, 52.8 months), all-cause death was significantly higher in group 3 compared with group 1 (adjusted hazard ratio, 2.97; 95%CI, 1.31–6.74; $P = 0.009$). Similar findings were observed in terms of the rates of death or myocardial infarction. Conclusions: Late DES failure is more likely to progress to acute myocardial infarction, aggressive angiographic patterns, and worse outcomes following retreatment. © 2014 Wiley Periodicals, Inc.

Key words: drug-eluting stent; restenosis; temporal patterns

INTRODUCTION

In-stent restenosis has markedly diminished since the introduction of drug-eluting stents (DES) [1–3]. However, the expanded use of DES in more complex procedures has increased the risk of DES failure including DES thrombosis or DES restenosis. Furthermore, the development of late lumen narrowing and DES failure is not uncommon on long-term follow-up [4,5]. Thus, DES failure is an important clinical problem even in the era of DES [6].

The angiographic patterns of restenosis are prognostically important, and nonfocal restenosis remains a therapeutic challenge because of the high risk of recurrence [7,8]. DES restenosis mostly occurs as focal patterns with stable symptoms [9,10]. However, nonfocal restenosis is often observed, and an appreciable propor-

Department of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea

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*Correspondence to: Seung-Jung Park, MD, PhD. Division of Cardiology, Asan Medical Center, University of Ulsan, 388-1 Pungnap-dong, Songpa-gu, Seoul, 138-736, Korea.
E-mail: sjpark@amc.seoul.kr

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tion of patients present with acute coronary syndrome [11–13]. The morphology of restenotic tissues also changes over time [14–20]. It is therefore likely that the patterns of DES failure differ depending on the time following DES placement. In this study, we investigate the temporal patterns of DES failure and the relationship to clinical outcomes in a large number of patients who developed DES failure.

METHODS

We identified 633 patients with 676 lesions who presented with their first instance of DES failure following percutaneous coronary intervention in the nonleft main native coronary arteries between October 2003 and December 2011. Patients were excluded if they had left main coronary intervention, prior coronary artery bypass surgery or concomitant valvular heart disease. All patient records were retrospectively retrieved from Asan Medical Center's clinical and angiographic laboratory database. Patients were divided into three groups according to the interval from index procedure to DES failure [17–19]: group 1 (early DES failure: $<$ 12 months), group 2 (late DES failure: 12–36 months), or group 3 (very late DES failure: $\geq$ 36 months). Previous DES (Cypher^{TM} stents, Cordis/Johnson and Johnson; Taxus^{TM} stents, Boston Scientific Corp) were used in 79.0% of patients, and new DES (Biomatrix^{TM} stent, Biosensors International; Endeavor^{TM} stent or Endeavor resolute^{TM} stent, Medtronic; Nobori^{TM} stent, Terumo Corporation; Promus Element^{TM} stent, Boston Scientific Corp; Xience^{TM} stent, Abbott Vascular) were used in the remaining 21% of patients.

Stent implantation was performed according to standard techniques, and stent selection was determined by the operator's discretion. Intravascular ultrasound guidance was routinely recommended during the procedure. Complete lesion coverage was recommended, as well as angiographic optimization with $<$ 20% residual stenosis as determined by visual estimation. Heparin was administered throughout the procedure in order to maintain an activated clotting time $\geq$ 250 sec. All patients were pretreated with aspirin and clopidogrel. Aspirin (100–200 mg/day) was used indefinitely, and clopidogrel (75 mg/day) was administered for $\geq$ 6–12 months.

Coronary angiography was performed before the procedure, after the procedure, and at the time of DES failure. All angiograms were submitted to the angiographic core analysis center (Asan Medical Center, Seoul, Korea) for analysis by independent angiographers. Digital angiograms were analyzed using an automated edge-detection system (CASS II, Pie Medical, Maastricht, Netherlands). Quantitative coronary angiographic measurements were obtained for the target lesions, stented segment, and margins that were 5-mm proximal and distal to the stent. The recorded angiographic variables included lesion length, stent length, reference vessel diameter, minimum lumen diameter, and percent stenosis. The angiographic patterns of DES failure were classified as focal stenosis ($<$10 mm), diffuse stenosis ($\geq$10mm), or total occlusion.

Follow-up information after retreatment was obtained by chart review and telephone interviews. Final follow-up status was ascertained between July and August 2013, and follow-up examinations were completed by 95.1% of patients. The unique personal identification number included in the National Population Registry of the Korea National Statistical Office was used to determine the vital status of the remaining 31 patients (4.9%) who could not be contacted.

DES failure was defined as restenosis or stent thrombosis following DES implantation [20,23]. Restenosis was defined as $>$50% luminal stenosis within the stent or within 5 mm of the stent edges on quantitative coronary angiography that is responsible for patient's symptoms or positive noninvasive functional tests. Stent thrombosis was defined as the definite occurrence of thrombotic events according to the classifications of the Academic Research Consortium [21]. Total occlusion at the stent site was attributed to restenosis if there was no obvious thrombus or acute myocardial infarction. All deaths were classified as cardiac unless an unequivocal noncardiac cause could be established. Unstable angina was defined as new onset, progression of previously identified angina (severity $\geq$ III according to the Canadian Cardiovascular Society Classification system), or rest angina. Acute myocardial infarction was diagnosed as the typical rise and fall of cardiac injury markers, sudden onset of resting chest pain lasting $>$ 20 min, or new ischemic changes on ECG [22]. The primary outcome of this study was death from any cause following treatment for DES failure. Secondary outcomes included a composite of death due to any cause or myocardial infarction, and a composite of death from any cause, myocardial infarction, or repeat target lesion revascularization.

Data are expressed as the mean $\pm$ SD for continuous variables or frequencies for categorical variables. Comparisons between groups were performed using the one-way ANOVA test for continuous variables or Fisher exact test for categorical variables. When one-way ANOVA was statistically significant, differences between data were determined using Tukey's test. Logistic regression analysis was used to identify the determinants of nonfocal DES failure. The cumulative event rates following treatment for DES failure were calculated using the Kaplan-Meier method. Differences

TABLE I. Baseline Characteristics at the Time of the Index Procedure

Characteristics	Group 1 ($n = 343$)	Group 2 ($n = 138$)	Group 3 ($n = 152$)	P
Age (y)	59.6 ± 10.1	58.6 ± 10.7	58.9 ± 10.0	0.652
Sex, male/female, n[a]	251/92	95/43	125/27	0.025
Body mass index, kg/m^2	24.7 ± 2.8	24.9 ± 2.9	25.1 ± 2.9	0.374
Current smoker	121 (35.3%)	44 (31.9%)	66 (43.4%)	0.099
Diabetes mellitus	118 (34.4%)	50 (36.2%)	45 (29.6%)	0.446
Hypertension	195 (56.9%)	76 (55.1%)	90 (59.2%)	0.773
Estimated GFR[b]	79.8 ± 29.6	79.5 ± 26.6	79.1 ± 24.4	0.976
Total cholesterol (mg/dL)	169.1 ± 39.7	166.5 ± 37.77	168.7 ± 34.9	0.801
Triglyceride (mg/dL)	146.1 ± 92.1	146.7 ± 93.6	151.8 ± 99.2	0.843
HDL cholesterol (mg/dL)	42.4 ± 11.8	41.8 ± 11.8	41.0 ± 10.7	0.533
Diagnosis[c]				0.013
Stable angina	191 (55.7%)	78 (56.5%)	79 (52.0%)	
Unstable angina	85 (24.8%)	48 (34.8%)	51 (33.6%)	
Acute myocardial infarction	67 (19.5%)	12(8.7%)	22 (14.5%)	
Target coronary arteries				0.245
Left anterior descending	187 (54.5%)	80 (58.0%)	78 (51.3%)	
Left circumflex	42 (12.2%)	21 (15.2%)	26 (17.1%)	
Right	112 (32.7%)	35 (25.4%)	44 (28.9%)	
Ramus intermedius	2 (0.6%)	2 (1.4%)	4 (2.6%)	
Previous myocardial infarction	29 (8.5%)	13 (9.4%)	10 (6.6%)	0.660
Left ventricular EF (%)	58.4 ± 8.1	57.5 ± 9.4	58.9 ± 9.9	0.347
Chronic total occlusion	25 (7.3%)	9 (6.5%)	10 (6.6%)	0.936
Bifurcation lesion	31 (9.0%)	10 (7.2%)	19 (12.5%)	0.287
Ostial lesion	25 (7.3%)	8 (5.8%)	12 (7.9%)	0.772
Multivessel coronary disease	154 (44.9%)	55 (39.9%)	71 (46.7%)	0.292
Types of drug-eluting stents[d]				<0.001
Previous	248 (72.3%)	112 (81.2%)	140 (92.1%)	
New	95 (27.7%)	26 (18.8%)	12 (7.9%)	

[a]Group 2 vs. Group 3, $P = 0.008$.
[b]Estimated GFR according to the Cockcroft-Gault method.
[c]Group 1 vs. Group 2, $P < 0.001$.
[d]Group 1 (or Group 2) vs. Group 3, $P < 0.025$. EF, ejection fraction; GFR, glomerular filtration rate. Previous drug-eluting stents included Cypher or Taxus stents, and new drug-eluting stents included biomatrix, endeavor, endeavor resolute, nobori, promus element, or xience stents.

in risk-adjusted clinical outcomes between groups were assessed using multivariate Cox proportional-hazards regression. Adjusted covariates included age, sex, diabetes mellitus, diagnosis at the index procedure, multivessel diseases, left ventricular function, type of DES, angiographic patterns of DES failure, stent thrombosis, diagnosis at the time of DES failure, and treatment modality for DES failure. A two-sided P value < 0.05 was required to indicate statistical significance.

RESULTS

DES failure occurred a median of 10.1 months (IQR = 6.9–35.3 months) after the index procedure. We identified 548 and 85 instances of DES restenosis (86.6%) and stent thrombosis (13.4%: 11 early instances [0–30 days poststent implantation], 14 late instances [30 days–12 months], and 60 very late instances [> 12 months]), respectively.

The baseline characteristics of the original lesions are summarized in Table I. The median age of the patients was 60.0 years (IQR = 52–67 years), and 74.4% of patients were men. There were no differences in terms of the baseline characteristics between the three groups, except sex, clinical diagnosis, and type of DES. Previous DES was more frequent in group 3.

Clinical presentations at the time of DES failure included stable angina (69.4% of patients), unstable angina (19.9%), and acute myocardial infarction (10.7%). As shown in Figure 1A, acute myocardial infarction was more common in patients who developed DES failure after 12 months than patients who presented earlier ($P < 0.001$). Likewise, the incidence of stent thrombosis was significantly higher in groups 3 and 2 in comparison with group 1 (24.3% vs. 16.7% vs. 7.3%, respectively; $P < 0.001$).

The quantitative coronary angiography data are summarized in Table II. We identified 348 instances of focal restenosis (55.0%), 174 instances of diffuse restenosis (27.5%), and 111 instances of total occlusion (17.5%). As shown in Figure 1B and Table II, the angiographic patterns of DES failure were significantly different between groups. The focal type was more frequently observed in group 1, whereas the nonfocal

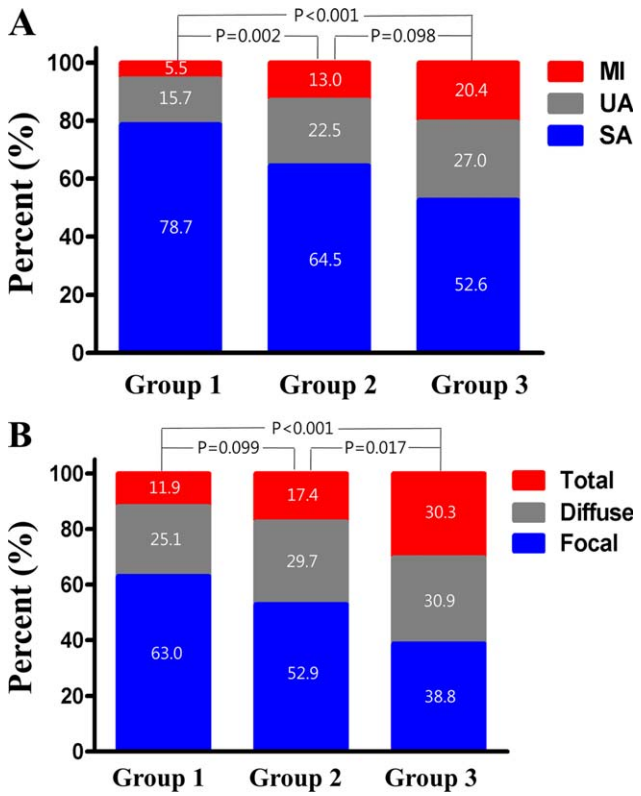

Fig. 1. (A) Clinical presentation at the time of DES failure and (B) angiographic patterns of DES failure. Late DES failure more frequently presented with acute myocardial infarction and aggressive angiographic patterns. MI, acute myocardial infarction; SA, stable angina; UA, unstable angina. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

type was more frequently found in groups 2 and 3. According to the multivariate analysis, time to DES failure (group 3 vs. group 1) and stent length were significant predictors of nonfocal DES failure (Table III).

DES failure was treated using medical treatment (n = 161), balloon angioplasty (n = 160), drug-eluting balloon angioplasty (n = 14), DES implantation (n = 256), or bypass graft surgery (n = 42). The median length of the follow-up period following treatment for DES failure was 52.8 months (IQR = 30.9–71.2 months). During follow-up, 43 deaths (27 cardiac and 16 noncardiac), 10 myocardial infarctions, and 45 target lesion revascularizations were identified. Death from any cause was significantly worse in group 3 in comparison with group 1 (adjusted hazard ratio = 2.97; 95% confidence interval [CI] = 1.31–6.74; P = 0.009) (Fig. 2A). The rate of all-cause-death or myocardial infarction was also significantly higher in group 3 compared with group 1 (adjusted hazard ratio = 2.74; 95% CI = 1.24–6.02; P = 0.012) (Fig. 2B). Similar trend was observed in terms of the rate of death, myocardial infarction, or target lesion revascularization (adjusted hazard ratio = 1.57; 95% CI = 0.88–2.81; P = 0.126) (Fig. 2C). In patients with DES restenosis, there were also worse clinical outcomes in group 3 compared with group 1: death from any cause (adjusted hazard ratio = 2.83; 95% CI = 1.18–6.79; P = 0.020), death or myocardial infarction (adjusted hazard ratio = 2.35; 95% CI = 1.01–5.48; P = 0.048), and death, myocardial infarction, or target lesion revascularization (adjusted hazard ratio = 1.60; 95% CI = 0.86–2.96; P = 0.133).

DISCUSSION

The results of our current study show that acute myocardial infarction is not uncommon following DES failure, and the late presentation of DES failure is more likely to develop into acute myocardial infarction. Furthermore, the angiographic patterns of DES failure were more aggressive in proportion to time from the index procedure. These findings support time-related differences in the patterns of DES failure, suggesting the notion that different biological mechanisms underlie late DES failure.

In-stent restenosis is generally believed to manifests as stable angina pectoris. However, restenosis is not always clinically benign. Among 1186 previous consecutive cases of clinical episodes of bare metal restenosis, 9.5% of patients presented with myocardial infarction and 26.7% presented with unstable angina that required hospitalization [23]. In our current study, clinical presentation at the time of DES failure included unstable angina in 19.9% of patients and acute myocardial infarction in 10.7% of patients. DES failure beyond 12 months after stent placement was commonly associated with an acute coronary syndrome, and up to 16.9% of patients presented with acute myocardial infarction. Furthermore, clinical outcomes following treatment of DES failure were significantly worse in these groups, thereby requiring new strategies to prevent late DES failure.

Most patients with restenosis demonstrate significant intimal hyperplasia at the minimum lumen site, and neointimal hyperplasia is the dominant mechanism of DES restenosis [24]. The focal type is the most common pattern of DES failure [8–10]. In our study, early DES failure within 12 months was more likely to present focally within the stent, supporting the notion that DES failure may be due to local problems with the stent at the affected point. In contrast, DES failure patterns were more diffuse and complex in the late and very late DES failure groups, suggesting different biological mechanisms of DES failure. Recently, the development of new atherosclerosis within stents was

TABLE II. Quantitative Coronary Angiographic Findings

Characteristics	Group 1 ($n = 343$)	Group 2 ($n = 138$)	Group 3 ($n = 152$)	P
Reference diameter (mm)	3.03 ± 0.54	2.89 ± 0.75	3.07 ± 0.54	0.879
Lesion length (mm)	31.1 ± 16.2	27.8 ± 18.1	28.0 ± 16.1	0.222
Stented length (mm)	37.5 ± 18.2	36.5 ± 18.0	35.9 ± 16.7	0.673
Stents per lesion	1.6 ± 0.9	1.6 ± 0.9	1.6 ± 0.9	0.835
Minimal lumen diameter (mm)				
Before procedure	0.86 ± 0.51	0.87 ± 0.52	0.91 ± 0.51	0.583
After procedure	2.31 ± 0.52	2.30 ± 0.70	2.40 ± 0.54	0.204
At follow-up[a]	0.90 ± 0.52	0.80 ± 0.55	0.62 ± 0.51	<0.001
Diameter stenosis (%)				
Before procedure	71.7 ± 16.7	67.5 ± 20.5	69.0 ± 17.9	0.098
After procedure	17.5 ± 11.5	14.3 ± 9.6	14.9 ± 9.9	0.094
At follow-up[b]	70.8 ± 15.8	73.8 ± 17.2	80.1 ± 16.3	<0.001
Pattern of DES failure[c]				<0.001
Focal	216 (63.0%)	73 (52.9%)	59 (38.8%)	
Diffuse	86 (25.1%)	41 (29.7%)	47 (30.9%)	
Total occlusion	41 (12.0%)	24 (17.4%)	46 (30.3%)	
Patients with DES restenosis[d]	$n = 318$	$n = 115$	$n = 115$	<0.001
Focal	208 (65.4%)	65 (56.5%)	51 (44.3%)	
Diffuse	85 (26.7%)	37 (32.2%)	40 (34.8%)	
Total occlusion	25 (7.9%)	13 (11.3%)	24 (20.9%)	

[a]Group 1 vs. Group 3, $P < 0.001$. Group 2 vs. Group 3, $P = 0.008$.
[b]Group 1 vs. Group 3, $P < 0.001$. Group 2 vs. Group 3, $P = 0.003$.
[c]Group 1 vs. Group 3, $P < 0.001$. Group 2 vs. Group 3, $P = 0.017$.
[d]Group 1 vs. Group 3, $P < 0.001$. Group 2 vs. Group 3, $P = 0.017$.

TABLE III. Predictors of Nonfocal DES Failure According to Logistic Regression Analysis

	Univariate Analysis			Multivariate Analysis		
Variables	OR	95%CI	P	OR	95%CI	P
Group 3 vs. Group 1	2.68	1.81–3.97	<0.001	2.78	1.87–4.13	<0.001
Stented length (mm)	1.01	1.00–1.02	0.007	1.01	1.01–1.02	0.003
Stented length > 40 mm	1.44	1.05–1.99	0.026			
Diabetes mellitus	1.33	0.95–1.86	0.095			
Reference vessel diameter	0.96	0.73–1.26	0.759			
Postintervention MLD	0.82	0.61–1.09	0.175			
Use of previous DES	1.17	0.80–1.72	0.420			

CI, confidence interval; DES, drug-eluting stent; MLD, minimal lumen diameter.

identified as an important mechanism of DES failure. Nakazawa et al. reported that in-stent neoatherosclerosis occurs in both bare metal stents and DES, though the latter demonstrates shorter implant duration [16]. In vivo imaging studies also demonstrate de novo atherosclerotic changes in the neointima following the implantation of either bare metal stents or DES [17–20]. Neoatherosclerotic lesions within stents may progress to tight stenosis and/or plaque rupture, leading to DES failure. Plaque rupture can expose the stent struts, in addition to the lipid core that triggers DES stent thrombosis. Early stent thrombosis (0–30-days post-stent implantation) is certainly related to incomplete stent healing. However, late stent thrombosis (30 days–12 months) or very late stent thrombosis (>12 months) is a complex phenomenon that may be related to acute thrombus formation due to either incomplete stent healing or in-stent plaque rupture from neoatherosclerosis. However, it is rather difficult to distinguish between stent thrombosis and in-stent restenosis because they are both mixed at the site of DES failure. Therefore, DES failure including stent thrombosis and restenosis may be a more comprehensive term rather than either one.

Various catheter-based revascularization strategies, including balloon angioplasty, angioplasty with a drug-eluting balloon, and DES implantation, are used to treat DES failure [25–27]. Despite advances in technology, however, the optimal treatment strategy still remains uncertain. In general, focal restenosis is believed to demonstrate the most favorable clinical outcomes following repeat intervention, whereas total restenosis is believed to demonstrate the poorest outcomes. In this study, focal DES failure tended to be

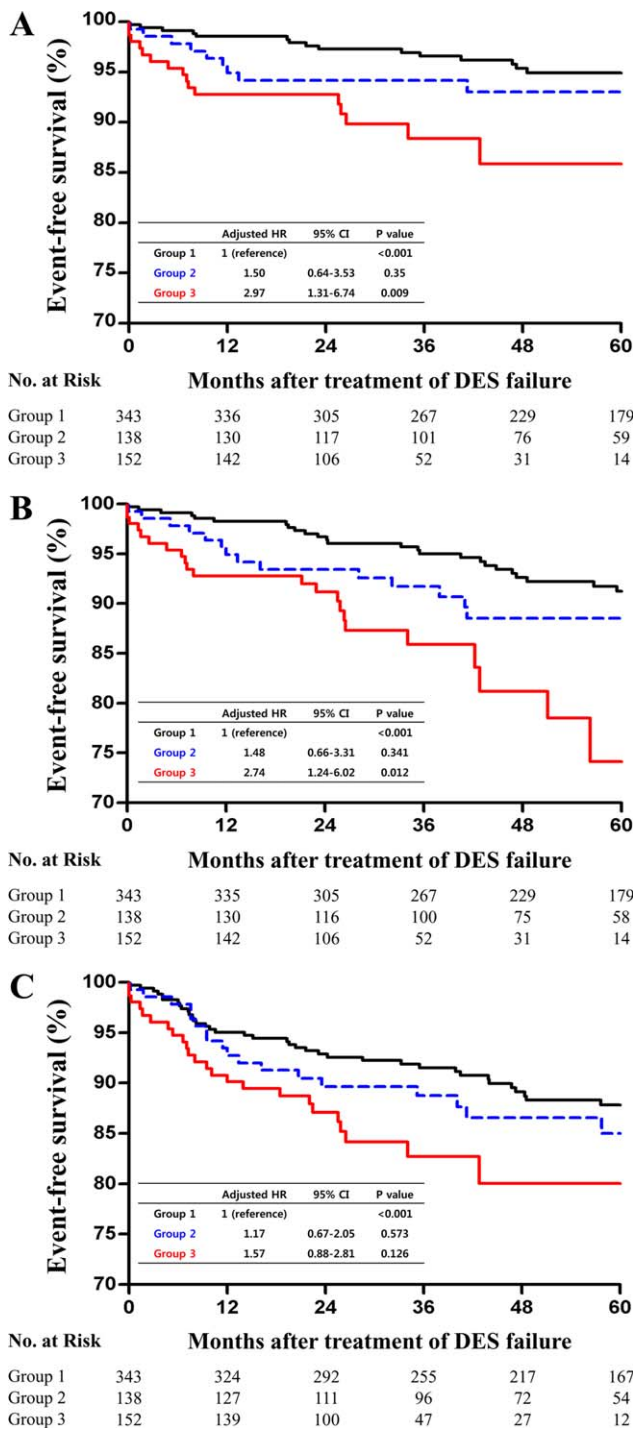

Fig. 2. Event-free survival curves following treatment for DES failure. (A) Death from any cause; (B) death from any cause or myocardial infarction; (C) death from any cause, myocardial infarction, or target lesion revascularization were higher in group 3 in comparison with group 1. HR, hazard ratio. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

associated with less re-revascularization compared with nonfocal DES failure following repeated interventions (HR 0.61, 95%CI 0.34–1.09, $P = 0.099$). In addition, time to DES failure is widely variable, and late and very late DES failure will become an increasingly common problem. Interestingly, time to DES failure is an important predictor of clinical outcomes following repeated interventions, suggesting that it should be considered when comparing treatment strategies for DES failure.

This study has several potential limitations. First, it was retrospective in design, which is an inherent limitation. We attempted to correct for differences in baseline characteristics using multivariate analysis. Second, invasive imaging data including optical coherence tomography were unavailable, and thrombi could not be accurately distinguished from neoatherosclerosis. Third, the majority of DES used in this study was previous DES. Fourth, data on duration of dual antiplatelet therapy are not available. Finally, the lack of a control group precluded the determination of any predictors of DES failure following DES implantation.

CONCLUSIONS

Late DES failure is more likely to progress to acute myocardial infarction, aggressive angiographic patterns, and worse outcomes following retreatment. These findings suggest time-related differences in the mechanisms of DES failure.

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