Clinical Investigation

Selective versus Exclusive Use of Drug-Eluting Stents in Treating Multivessel Coronary Artery Disease:

A Real-World Cohort Study

Arsha Karbassi, MD
Seyed Ebrahim Kassaian, MD, FACC
Hamidreza Poorhosseini, MD
Mojtaba Salarifar, MD
Arash Jalali, PhD
Ebrahim Nematipour, MD
Elham Hakki Kazazi, MD
Mohammad Alidoosti, MD
Ali Mohammad Hajizeinali, MD, FSCAI
Masoumeh Lotfi Tokaldani, MD, MPH

There have been attempts to find new approaches to the treatment of multivessel coronary artery disease without increasing adverse events. Deployment of drug-eluting stents (DES) for complex lesions and bare-metal stents (BMS) for simpler lesions, although already in wide use, has not been well supported by clinical study.

A cohort of 1,658 patients who underwent multivessel percutaneous coronary intervention from March 2003 through June 2011 was studied for 1 year. These patients were divided into 3 groups: BMS only (599 patients); DES only (481 patients); and hybrid stenting (578 patients). Baseline characteristics were similar except for hyperlipidemia and moderate-to-severe mitral regurgitation, which were more frequent in the DES and hybrid groups, respectively. Lesion characteristics were more complex in the DES group, compared with the other groups: more B2/C type lesions, longer stents, and smaller reference-vessel diameters (P <0.001). The rates of major adverse cardiac events (MACE) at 1 year were similar between the groups (BMS=5.2%, hybrid=3.9%, and DES=3.4%; P=0.248). Subgroup analysis yielded no differences in death, nonfatal myocardial infarction, target-vessel revascularization, or target-lesion revascularization. On multivariable analysis, the strongest predictors of 1-year MACE were percutaneous intervention complicated by dissection, renal failure, left ventricular ejection fraction below 0.40, mean lesion length, reference vessel diameter, and percutaneous intervention on the left circumflex coronary artery. The latter two had inverse relationships with MACE.

In conclusion, implanting the DES for more complex lesions and the BMS for simpler lesions seems more sensible than the exclusive use of the DES or the BMS. ***(Tex Heart Inst J 2014;41(5):477-83)***

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From: *Departments of Interventional Cardiology (Drs. Alidoosti, Hajizeinali, Karbassi, Kassaian, Nematipour, Poorhosseini, and Salarifar) and Research and Biostatistics (Drs. Jalali, Hakki, and Lotfi), Tehran Heart Center, Tehran University of Medical Sciences, 1411713138 Tehran, Iran*

Address for reprints: *Seyed Ebrahim Kassaian, MD, FACC, Department of Interventional Cardiology, Tehran Heart Center, Tehran University of Medical Sciences, N. Kargar St., 1411713138 Tehran, Iran*

E-mail: *ekassaian@yahoo.com*

The drug-eluting stent (DES), in comparison with the bare-metal stent (BMS), has been associated with a reduction both in the incidence of restenosis and in the need for repeat interventions.[1-4] However, the benefit of the DES appears to be confined to lowering the risks of repeat interventions, because mortality rates and the risk of myocardial infarction (MI) have not been lessened by the DES.[5,6] Other issues that should be considered in patients with DES implants are late thrombosis in a small but significant number of patients[7-9] and the need for prolonged dual antiplatelet therapy.

In multivessel percutaneous coronary intervention (PCI), there have been attempts to find new approaches to revascularization in an effort to minimize cost, late thrombosis, and the risk of early discontinuation of dual antiplatelet therapy. These considerations have led to the development of a practice in which DES is used for complex, high-risk lesions and BMS for simple and low-risk lesions, even in the same patient.[10] Although this approach already has been applied in the real world, its outcome has yet to be fully evaluated.

The aim of this study was to investigate the clinical impact of the DES when used in combination with the BMS in the percutaneous treatment of multivessel coronary artery disease (CAD). We compared the results of 3 different approaches in the

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treatment of multivessel-CAD patients within a large registry: BMS only, DES and BMS in the same patient (hybrid stenting), and DES only.

Patients and Methods

We studied and followed clinically for up to one year a cohort of 1,658 patients who had undergone multivessel PCI from March 2003 through June 2011 at Tehran Heart Center, a tertiary university hospital. Patients who had undergone PCI for acute MI and left main coronary artery lesions were excluded from the study. Demographic, clinical, and procedural data were obtained from the dedicated PCI registry forms of the Tehran Heart Center and reviewed by independent research personnel beginning in July 2012.

The patients had received at least 2 stents in 2 different vascular territories. According to the type of stent, the patients were divided into 3 groups: the BMS-only group (599 patients), the hybrid group (578 patients), and the DES-only group (481 patients).

Coronary angioplasty had been performed in the conventional manner. Interventional approaches and device decisions, including the use of DES, direct stenting, before or after dilation, intravascular ultrasonography, and choices of periprocedural adjunctive antiplatelet therapy and antithrombotic regimen, had been left to the discretion of the attending physician. All the patients had received aspirin (325 mg) before the intervention and continued thereafter a lifelong regimen of 80 to 100 mg/d. Clopidogrel (300–600-mg loading dose) was prescribed and was continued with a dose of 75 mg/d for at least one month in the BMS group and one year in the DES group. The anticoagulation regimen consisted of either weight-adjusted heparin or low-molecular-weight heparin. Other medications, including statins, β-blockers, and angiotensin-converting enzyme inhibitors, were given according to guidelines. Cardiac-specific enzymes were routinely evaluated after the interventional procedure.

Endpoints for analysis were major adverse cardiac events (MACE) from the time of PCI up to the one-year follow-up. We defined MACE as a composite of death, nonfatal MI, and target-vessel revascularization (TVR). Target-lesion revascularization and TVR were defined as repeat intervention of the treated lesion or vessel, respectively. Deaths were not distinguished by cause. In addition, MI and periprocedural MI were classified and reported in accordance with the universal definition of MI.[11] Lesions were classified according to the American College of Cardiology/American Heart Association guidelines for B2/C and non-B2/C type lesions.[12] Lesion length and reference-vessel diameter (RVD) were estimated visually by the operators. Quantitative coronary analysis was available if required by the attending physician. In this study, DES comprised paclitaxel-, sirolimus-, everolimus-, and zotarolimus-eluting stents. Left ventricular ejection fraction (LVEF) was measured by means of echocardiography or angiography during each patient's hospitalization.

Statistical Analysis

The data are presented as mean ± SD for quantitative variables, and as frequencies and percentages for categorical variables. The continuous variables between the 3 groups (of BMS, hybrid, and DES patients) were compared by using the one-way analysis of variance or the Kruskal-Wallis test (when the data did not meet the normality assumption) and were compared between the 2 groups (of hybrid and DES) by using the Student *t* test or the Mann-Whitney test. Categorical variables were compared with use of the χ^2 test or the Fisher exact test, as appropriate. The Kaplan-Meier method was used in calculating survival, and the log rank test was used in comparing the groups. A multivariable Cox proportional hazards model with the backward variable selection method (0.1 for removal and 0.05 for entry probabilities) was applied in detecting multiple predictors of MACE in each group. The hazard ratio (HR) was presented with its 95% confidence interval (CI). Variables in the univariate analyses with a *P* value ≤0.15 were selected to enter the multivariable model for each group. The proportional hazards assumption was examined by using the χ^2 test of correlation coefficient between the transformed survival time and the scaled Schoenfeld residuals through a "Survival" package.[13,14] No statistically significant violation of the proportional hazards assumption was observed in the multivariable analyses. The analyses were performed with use of SPSS software version 15.0 for Windows (IBM Corporation; Armonk, NY) and R software.[15] A *P* value <0.05 was considered statistically significant.

Results

The BMS group had more patients with histories of renal failure and LVEFs below 0.40. The hybrid group had more patients with hypertension, histories of MI, and histories of cerebrovascular accident. The DES group had more men and more patients with histories of diabetes mellitus, cigarette smoking, hyperlipidemia, previous PCI, and previous coronary artery bypass grafting (CABG) (Table I).

In regard to procedural and lesion characteristics, the average numbers of lesions per patient and stents implanted per patient were higher in the hybrid group than in the other 2 groups. The hybrid group encompassed more patients with 3-vessel disease, bifurcation lesions, and periprocedural MI. The DES group had more patients with B2/C type lesions, longer lesions and stents, smaller RVDs, and more occlusions. The BMS group had larger RVDs and shorter stents. This group

TABLE I. Baseline Characteristics of the 1,658 Patients

Variable	BMS (n=599)	Hybrid (n=578)	DES (n=481)	*P* Value	*P* Value, Hybrid vs DES
Age (yr)	58.18 ± 10.84	58.36 ± 10.78	56.92 ± 10.46	0.081	0.29
Male	414 (69.9)	422 (73)	359 (74.6)	0.211	0.549
Body mass index (kg/m^2)	27.91 ± 4.44	27.57 ± 4.33	27.27 ± 4.21	0.1	0.308
Serum creatinine (mg/dL)	1.14 ± 0.6	1.13 ± 0.47	1.11 ± 0.46	0.208	0.125
LDL cholesterol (mg/dL)	109.3 ± 42.58	99.69 ± 37.06	102.71 ± 40.09	0.006	0.406
Diabetes mellitus	128 (21.4)	138 (23.9)	132 (27.4)	0.067	0.185
Hypertension	259 (43.2)	253 (43.8)	199 (41.4)	0.717	0.432
Cigarette smoker	120 (20)	141 (24.4)	124 (25.8)	0.06	0.604
Hyperlipidemia	401 (66.9)	365 (63.1)	332 (69)	0.118	0.045
Family history of CAD	126/559 (21)	127 (22)	125 (26)	0.131	0.127
History of MI (including NSTEMI)	257/594 (43.2)	277/570 (48.6)	199/471 (42.2)	0.641	0.358
Previous PCI	25 (4.2)	40 (6.9)	35 (7.3)	0.056	0.822
Previous CABG	14 (2.3)	20 (3.5)	18 (3.7)	0.361	0.806
History of CVA	1/594 (0.2)	4/570 (0.7)	1/471 (0.2)	0.26	0.256
Renal failure	10 (1.7)	9 (1.6)	6 (1.2)	0.846	0.671
LVEF ≤0.40	53/531 (10)	50/527 (9.5)	28/443 (6.3)	0.098	0.071
Moderate-to-severe mitral regurgitation	15 (2.5)	30 (5.2)	16 (3.3)	0.001	0.198

BMS = bare-metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CVA = cerebrovascular accident; DES = drug-eluting stent; LDL = low-density-lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention

Data are presented as mean ± SD or as number and percentage. $P<0.05$ was considered statistically significant.

also had more PCI procedures that were followed by dissection (Table II).

The MACE at one year was similar in the 3 groups. Subgroup analysis yielded no difference in terms of nonfatal MI, target-lesion revascularization, TVR, and death (Table III; Figs. 1 and 2). In the univariate analysis, the predictors of MACE included cigarette smoking, hyperlipidemia, renal failure, previous PCI, LVEF <0.40, bifurcation lesion, dissection as a sequela to PCI, PCI of the left circumflex coronary artery (LCx) territory, RVD, and mean lesion length. In the multivariable analysis, the strongest predictors of one-year MACE in BMS group were renal failure, LVEF <0.40, and mean lesion length. In the hybrid group, MACE predictors were dissection as a sequela to PCI, RVD, and PCI of the LCx territory. The latter two had inverse relationships with MACE. In the DES group, PCI complicated by dissection was the only predictor of MACE (Table IV).

Discussion

The optimal strategy for the treatment of patients with multivessel CAD has been a matter of debate. Earlier studies, such as the Arterial Revascularization Therapies Study (ARTS I) and the Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple-Vessel Disease (ERACI II) trials, compared the BMS to CABG and showed that the frequencies of death and MI were similar in the 2 arms, although freedom from repeat procedures and angina was superior in the surgical arm.[16,17] After the introduction of the DES in clinical practice, trials such as ARTS II and ERACI III tracked the DES in the treatment of multivessel CAD and showed that the TVR rate was lower than that of the BMS—and comparable to that of the surgical arms of ARTS I and ERACI II.[18,19] In ARTS II and ERACI III, all lesions were treated with the DES; however, it still is not clear whether all lesions in patients with multivessel PCI should be treated in such a manner.

Issues that should be taken into consideration when contemplating the use of multiple DESs in a patient include a higher incidence of subacute and late stent thrombosis in patients treated with the DES, compared with the BMS.[20] Results from a pooled analysis, including 10 randomized studies, showed that stent thrombosis was related to the total lengths and numbers of DESs implanted.[21] The clinical benefits of the DES,

TABLE II. Procedural and Lesion Characteristics

Variable Lesions (N=3,790) Patients (N=1,658)	BMS (1,358 Lesions in 599 Patients)	Hybrid (1,391 Lesions in 578 Patients)	DES (1,041 Lesions in 481 Patients)	*P* Value	*P* Value, Hybrid vs DES
Lesions per patient	2.26 ± 0.52	2.4 ± 0.63	2.16 ± 0.42	<0.001	<0.001
Stents per patient	2.24 ± 0.5	2.46 ± 0.7	2.18 ± 0.44	<0.001	<0.001
Target vessel (lesion)	—	—	—	<0.001	0.157
LAD	464 (34.2)	540 (38.8)	421 (40.4)	—	—
LCx	458 (33.7)	376 (27)	283 (27.2)	—	—
RCA	430 (31.7)	454 (32.6)	331 (31.8)	—	—
SVG	6 (0.4)	21 (1.5)	6 (0.6)	—	—
Ostial/proximal LAD*	176/422 (41.7)	241/479 (50.3)	234/398 (58.8)	<0.001	0.012
ACC/AHA lesion type	—	—	—	<0.001	<0.001
B2/C	819/1,314 (62.3)	998/1,385 (72)	829/1,040 (79.7)	—	—
C	508/1,314 (38.7)	761/1,385 (54.9)	707/1,040 (68)	—	—
Type C lesions treated by DES	0	70.1	100	—	—
Lesion length (mm)	17.15 ± 7.68	20.65 ± 10.2	22.33 ± 9.65	<0.001	<0.001
RVD (mm)	3.16 ± 0.53	3.15 ± 0.48	3.02 ± 0.39	<0.001	<0.001
Stent length (mm)	18.86 ± 6.81	23.37 ± 9.96	26.04 ± 9.15	<0.001	<0.001
Multivessel disease	—	—	—	0.03	0.006
2-vessel	396 (66.1)	353 (61.1)	330 (68.6)	—	—
3-vessel	203 (33.9)	225 (38.9)	151 (31.4)	—	—
Direct stenting	769/1,269 (60.6)	733/1,328 (55.2)	471/991 (47.5)	<0.001	<0.001
Patients with bifurcation lesion	69 (11.5)	95 (16.4)	78 (16.2)	0.028	0.923
Patients with total occlusion	78 (13)	82 (14.2)	73 (15.2)	0.595	0.65
Postdilation balloon diameter (mm)	3.42 ± 0.52	3.3 ± 0.5	3.15 ± 0.41	<0.001	<0.001
Postdilation pressure (mmHg)	16.78 ± 3.29	17.11 ± 3.47	17.14 ± 3.74	0.162	0.654
PCI followed by dissection	33 (5.5)	13 (2.2)	4 (0.8)	<0.001	0.54
Periprocedural MI	27/581 (4.6)	44/567 (7.8)	33/474 (7)	0.083	0.624

ACC/AHA = American College of Cardiology/American Heart Association; BMS = bare-metal stent; DES = drug-eluting stent; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter; SVG = saphenous vein graft

*Number of patients with LAD lesion that involved ostium or proximal part of the vessel.

Data are presented as mean ± SD or as number and percentage. $P < 0.05$ was considered statistically significant.

TABLE III. Clinical Events at One Year in the 1,658 Patients

Variable	BMS (n=599)	Hybrid (n=578)	DES (n=481)	*P* Value	*P* Value, Hybrid vs DES
Nonfatal MI	10/555 (1.8)	8/549 (1.4)	3/461 (0.6)	0.251	0.223
TLR	6/555 (1.1)	10/557 (1.8)	3/464 (0.6)	0.243	0.102
TVR	18/555 (3.2)	14/557 (2.5)	8/464 (1.7)	0.238	0.382
Death	8/555 (1.4)	4/557 (0.7)	5/464 (1.1)	0.456	0.552
MACE	29/555 (5.2)	22/557 (3.9)	16/464 (3.4)	0.248	0.661

BMS = bare-metal stent; DES = drug-eluting stent; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target-lesion revascularization; TVR = target-vessel revascularization

Data are presented as number and percentage. $P < 0.05$ was considered statistically significant.

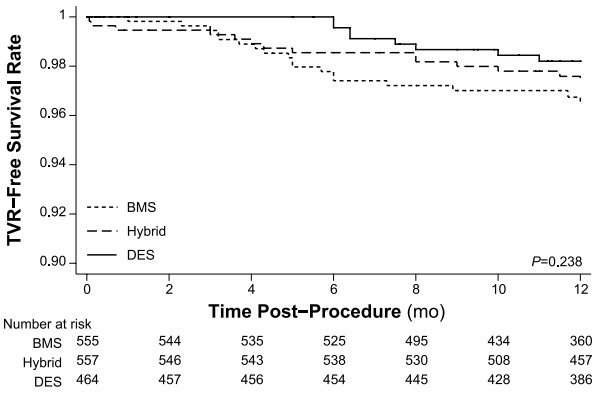

Fig. 1 *Kaplan-Meier curves for freedom from target-vessel revascularization (TVR).*

BMS = bare-metal stent; DES = drug-eluting stent

P *<0.05 was considered statistically significant.*

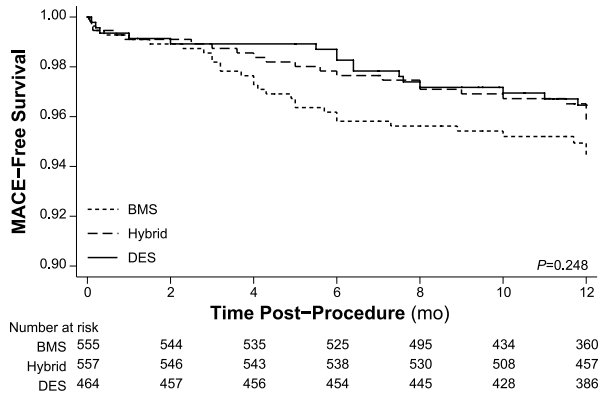

Fig. 2 *Kaplan-Meier curves for freedom from major adverse cardiac events (MACE).*

BMS = bare-metal stent; DES = drug-eluting stent

P *<0.05 was considered statistically significant.*

TABLE IV. Multiple Predictors of Major Adverse Coronary Events

Group	Predictors	Hazard Ratio	95% CI	*P* Value
Bare-metal stent	Renal failure	8.704	2.597–29.174	<0.001
	LVEF <0.40	2.72	1.083–6.832	0.033
	Mean lesion length	1.047	1.000–1.097	0.053
Hybrid	Dissection	6.223	1.433–27.025	0.015
	LCx territory	0.207	0.082–0.522	0.001
	Reference vessel diameter	0.086	0.018–0.413	0.002
Drug-eluting stent	Dissection	11.317	1.493–85.799	0.019

CI = confidence interval; LCx = left circumflex coronary artery; LVEF = left ventricular ejection fraction

P <0.05 was considered statistically significant.

in comparison with those of the BMS, were reduced in the ERACI III registry after the first year's report. Follow-up studies of this registry illustrated that, despite a continued lower incidence of major adverse cardiac and cerebrovascular event rates, the initial advantage of the DES over the BMS appeared to decrease with time.[22]

The issues that might affect a patient's receiving multiple DESs have led to the proposal of a hybrid approach in which both the BMS and the DES are used for the treatment of multivessel CAD. Although this approach is used in everyday practice (approximately in 11%–13% of all PCI procedures), the outcomes have yet to be fully evaluated, because this group of patients has thus far been excluded from randomized clinical trials.[23,24]

A few studies have indeed evaluated the hybrid approach to the treatment of multivessel PCI. In a study by Varani and colleagues,[10] the data of the patients enrolled in the Registro REgionale AngiopLastiche Emilia-Romagna (REAL) were screened, and all the multivessel PCI procedures from July 2002 through December 2004 were identified and analyzed. The multivessel PCI procedures (1,726 patients) were divided into 3 groups: BMS only, DES only, and mixed. The DESs consisted of sirolimus- and paclitaxel-eluting stents. The investigators reported no significant differences in 1-year outcomes between these groups, when the DES was used in high-risk patients and lesions. The cumulative MACE were BMS (19.3%), mixed (17.9%), and DES (16.4%) (P=0.447).

Another study, performed on the REAL registry patients from 2003 through 2006, included 2,898 patients with multivessel PCI, who were monitored for 2 years. In comparison with the BMS group, both the DES and the mixed groups were associated with a 2-year reduction in adverse clinical outcomes, especially in patients at high risk of TVR. Exclusive DES use was not superior to the mixed approach. Furthermore, cumulative MACE at 2 years was DES (18.9%), mixed (19%), and BMS (24.2%) (P=0.003).[24]

TABLE V. Comparison of Clinical Events at One Year

Group	Varani E, et al.[10] (N=1,726)	Syed AI, et al.[25] (N=2,065)	Current Study (N=1,658)
BMS	939 (54.4)		559 (36.1)
B2/C lesion type	55.30%		819/1,314 (62.3)
TVR	13.10%	—	18/555 (3.2)
MACE	19.30%		29/555 (5.2)
Hybrid	499 (28.9)	698 (33.8)	578 (34.8)
B2/C lesion type	65.70%	430/1,795 (24)*	998/1,385 (72)
TVR	12.40%	72/667 (10.8)	14/557 (2.5)
MACE	17.90%	120/698 (17.2)	22/557 (3.9)
DES	288 (16.6)	1,367 (66.1)	481 (29)
B2/C lesion type	62.90%	545/3,190 (17.1)*	829/1,040 (79.7)
TVR	11.60%	130/1,339 (9.7)	8/464 (1.7)
MACE	16.40%	200/1,367 (14.6)	16/464 (3.4)

BMS = bare-metal stent; DES = drug-eluting stent; MACE = major adverse cardiac event; TVR = target-vessel revascularization

*Type C lesion

Data are presented as number (percentage) unless otherwise specified.

Syed and colleagues[25] studied the hybrid strategy versus the exclusive implantation of DESs for multivessel PCI. A cohort of 2,065 patients was followed up clinically. In that study, the DESs comprised sirolimus- and paclitaxel-eluting stents. At one year, there was no significant difference in TVR-MACE (hybrid=17.2% vs DES=14.6%; *P*=0.128). In multivariable analysis, hybrid PCI was not a predictor of TVR-MACE. Rather, the strongest predictors of MACE were hypertension, black race, and left anterior descending coronary artery disease. The investigators concluded that a hybrid stenting approach should be considered for patients with multivessel PCI, because it could lower procedural costs without increasing adverse events.

We studied 1,658 patients who had multivessel PCI, by dividing them into 3 groups. There was no statistical difference in 1-year MACE between the groups. Although the lesions treated in the DES and hybrid groups were more complex than those in the BMS group, the outcomes were comparable. Therefore, selective use of the DES in treating more complex lesions confers results similar to those of treating less complex lesions with the BMS.

The predictors of MACE in our study included PCI followed by dissection, renal failure, LVEF <0.40, and mean lesion length. Both larger RVD and PCI performed for the LCx territory had inverse relationships with MACE. Regarding the latter, we performed a meticulous subanalysis in an effort to find a coherent explanation; however, this finding remains an enigma.

Our finding regarding 1-year MACE rates in the 3 different groups is consistent with those of other studies (Table V). The differences in MACE predictors between various studies are due to variations in baseline, as well as to procedural and lesion characteristics. Our study recruited patients who underwent multivessel PCI from 2003 through 2011. This time frame provided us with the opportunity to use not only sirolimus- and paclitaxel-eluting stents but also the newer everolimus- and zotarolimus-eluting stents in both the DES and hybrid groups, which is unique in comparison with earlier studies.

Limitations. The present study has the inherent limitations of a retrospective analysis. We excluded primary PCI patients in whom PCI was performed emergently, which might have affected our MACE rates. In addition, the selection of the revascularization strategy was at the discretion of the operators; this bias was partially obviated by our multivariable analysis. The exact percentage of compliance with antiplatelet therapy during follow-up could not be calculated, because of missing data.

Conclusion. We showed that, in patients with both complex and simple lesions requiring multivessel PCI, the strategy of implanting the DES for more complex lesions and the BMS for simpler lesions seems to be more sensible than the exclusive use of either the DES or the BMS. This method can lower procedural costs without an increase in adverse events. Our findings support other studies that have evaluated the hybrid strategy in the treatment of multivessel PCI. A randomized clinical trial is suggested to confirm the findings of this study.

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