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Impact of drug-eluting stent-associated coronary artery spasm on 3-year clinical outcomes: A propensity score matching analysis

Jabar Ali ^{a,b}, Seung-Woon Rha ^{c,*}, Byoung Geol Choi ^d, Jae Kyeong Byun ^d, Se Yeon Choi ^d, Jin Ah Cha ^e, Soohyung Park ^c, Kyuho Lee ^c, Seungmin Back ^c, Jieun Lee ^c, Dong Oh Kang ^c, Jah Yeon Choi ^c, Seung-Young Roh ^c, Jin Oh Na ^c, Cheol Ung Choi ^c, Jin-Won Kim ^c, Eung Ju Kim ^c, Chang Gyu Park ^c, Hong Seog Seo ^c, Mohammad Wasim ^f, Zair Hassan ^f

^a MBBS, MCPS (medicine), FCPS Cardiology, Fellowship in Coronary and Peripheral Intervention, Seoul, South Korea

^b Assistant Professor Cardiology, Department of Cardiology, MTI Lady Reading Hospital Peshawar, Pakistan

^c Cardiovascular Center, Korea University Guro Hospital, Seoul, South Korea

^d Cardiovascular Research Institute, Korea University College of Medicine, Seoul, South Korea

^e Department of Biomedical Sciences, Korea University Graduate School, Seoul, South Korea

^f MBBS, Postgraduate Trainee Cardiology Department of Cardiology, Lady Reading Hospital, Peshawar Pakistan

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ABSTRACT

Background: It has been reported that significant endothelial dysfunction or clinically evident vasospasm can be associated with drug-eluting stents (DESs). However, the impact of DES associated coronary artery spasm (CAS) on long-term clinical outcomes has not been fully elucidated as compared with those of patients with vasospastic angina.

Methods: A total of 2797 consecutive patients without significant coronary artery lesion (<70%), who underwent the Acetylcholine (Ach) provocation test, were enrolled between Nov 2004 and Oct 2010. DES-associated spasm was defined as significant CAS in proximal or distal to previously implanted DES site at follow-up angiography with Ach test. Patients were divided into two groups (DES-CAS; n = 108, CAS; n = 1878). For adjustment, propensity score matching (PSM) was done (C-statistics = 0.766, DES-CAS; n = 102, CAS; n = 102). SPSS 20 (Inc., Chicago, Illinois) was used to analyze this data.

Results: Baseline characteristics were worse in the DES-CAS group. After PSM, both baseline characteristics and the Ach test results were balanced except higher incidence of diffuse CAS and ECG change in the DES-CAS group. During Ach test, the incidence of diffuse spasm (93.1% vs. 81.3%, p = 0.012) and ST-T change (10.7% vs. 1.9%, p = 0.010) were higher in the DES-CAS group. At 3-year, before and after adjustment, the DES-CAS group showed a higher incidence of coronary revascularization (9.8% vs. 0.0%, p = 0.001), recurrent chest pain requiring follow up coronary angiography (CAG, 24.5% vs. 7.8%, p = 0.001) and major adverse cardiac events (MACEs, 9.8% vs. 0.9%, p < 0.005).

Conclusion: In this study, DES associated CAS was associated with higher incidence of diffuse spasm, ST-T change and adverse 3-year clinical outcomes. Special caution should be exercised in this particular subset of patients.

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* Corresponding author. Cardiovascular Center, Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, Seoul, 08308, South Korea.

E-mail addresses: dr.jabarali78@gmail.com (J. Ali), swrha617@yahoo.co.kr (S.-W. Rha), trv940@gmail.com (B.G. Choi), jkyun0228@naver.com (J.K. Byun), nenid00@naver.com (S.Y. Choi), jinahcha@naver.com (J.A. Cha), shp503@naver.com (S. Park), yoloel@naver.com (K. Lee), hewleft@naver.com (S. Back), ch93lje@naver.com (J. Lee), gelly9@naver.com (D.O. Kang), kekeruki@gmail.com (J.Y. Choi), rsy008@gmail.com (S.-Y. Roh), koolup93@gmail.com (J.O. Na), wmagpie@korea.ac.kr (C.U. Choi), kjwmm@korea.ac.kr (J.-W. Kim), withnoel@hanmail.net (E.J. Kim), parkcg@kumc.or.kr (C.G. Park), mdhsseo@korea.ac.kr (H.S. Seo), drmwasim107@gmail.com (M. Wasim), zair.hassan7272@gmail.com (Z. Hassan).

1. Introduction

Drug eluting stents (DES) use has contributed to a significant reduction in restenosis and target vessel revascularization rates in comparison to bare metal stents (BMS). Although all DES approved for different clinical uses, proved to reduce restenosis, there is marked difference between various drug–polymer–device combinations that may result in different biological responses and eventually impact on net clinical outcomes.^{1–3} Human studies (both in vivo and autopsy studies) have shown a number of possible mechanisms for stent thrombosis; it may involve poor endothelialization, fibrin deposition, and local inflammatory or hypersensitivity reaction.^{4–8} In recent in vivo studies, it has been shown that both sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) were associated with paradoxical coronary artery vasoconstriction distal to the stented segments 6–9 months after the implantation.^{9–12} Whereas in one study relatively preserved endothelial dependent vasomotor function was shown 9 months after sirolimus-eluting stents implantation.¹³ But studies have shown mixed results regarding the prognosis in patients with coronary artery spasm (CAS) in native coronary arteries.^{14,15}

There is no study till date, comparing the DES associated spasm with native CAS. In the present study, we aimed to determine the 3-year clinical outcomes of patients with DES associated CAS in comparison to those of patients with native CAS.

2. Methods

2.1. Patient's population

In this study, data for 2797 consecutive patients with insignificant coronary artery disease (CAD, <70% diameter stenosis visually), who underwent Ach test between November 2004 to October 2010, were analyzed. Out of 2797 patients 1878 were having native CAS while 108 patients were having DES associated spasm. They were divided into two groups, that with significant spasm on native coronary artery called CAS (CAS group), and that significant spasm on stented coronary artery was called DES associated spasm (DES CAS Group). For adjustment, propensity score matching (PSM) was done (C-statistics = 0.766, DES-CAS; n = 102, CAS; n = 102).

2.2. Procedure

All patients with insignificant lesions in coronary arteries were supposed to undergo acetylcholine (Ach) provocation test after giving a written and informed consent. This study was according to the Declaration of Helsinki. Nitrates, calcium channel blockers (CCB), beta blockers (BB), angiotensin-converting enzyme inhibitors (ACEI), and other vasodilators or vasoconstrictors were stopped at least 72 h before coronary angiography. Before Ach provocative test, control coronary angiography (CAG) was obtained in each patient in an appropriate projection to ensure best separation of branches of coronary artery, and then CAG was done in the same projection after Ach injection.

2.3. Acetylcholine provocation test

Ach provocation test was conducted by injection of incremental doses of acetylcholine 20 (A1), 50 (A2) and 100 (A3) µg through a diagnostic catheter into coronary artery over a 1 min period with 5 min intervals to the maximum tolerated dose under continuous monitoring of electrocardiogram (ECG) and blood pressure, that was followed by intracoronary injection of Nitroglycerin 200 µg (glyceroltrinitrate, Schwarz Pharma, Monheim, Germany) if there was significant vasoconstriction of the epicardial coronary artery or

patients developed chest discomfort or ECG showed ST-T changes, suggestive of ischemia. Ach provocation test was not performed if the patients were unstable, severe chronic pulmonary obstruction, severe renal insufficiency, and allergy to iodinated contrast media.

2.4. Study end points

Study end points were 3-year cumulative clinical events that included total mortality, cardiac death, myocardial infarction (MI), percutaneous coronary intervention (PCI), and cerebrovascular accident (CVA) and major adverse cardiac events (MACE). MACE was defined as the composite of all-cause mortality, PCI and MI.

2.5. Quantitative analysis

All Ach provocation test were quantitatively analyzed with QCA- (FD-20, Phillips, Amsterdam, The Netherlands) by two independent observers. Ach provocation test was considered positive if there was ≥70% focal or diffuse narrowing of any epicardial coronary artery with Ach injection during systolic images compared with the relaxed state after intracoronary injection of nitroglycerine, with or without chest discomfort or ischemic ECG changes.

2.6. Statistics

SPSS 20 (Inc., Chicago, Illinois) was used to analyze data. Continuous variables were expressed as means ± standard deviation and were compared using Student's *t*-test. Categorical data were expressed as percentages and were compared using chi-square statistics or Fisher's exact test. PSM analysis was performed using the Cox-regression model. We tested all available variables that could be of potential relevance: age, male, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, current smokers, current alcoholics angiographic and clinical parameters during provocation test (location of CAS or MB, severity or length of CAS, EKG change, and chest pain during provocation test). Multivariate Cox proportional hazard models were used to compare clinical endpoints between groups. Kaplan-Meier analysis was performed to estimate the cumulative incidence of clinical events. A two-tailed *T* test *p*-value of <0.05 was considered to be statistically significant. Data was expressed as mean ± standard deviations. All the statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Baseline clinical, laboratory and angiographic characteristics between the two groups, the DES- CAS and CAS group, were different before propensity score match (PSM), but after PSM they were well matched, except that there was higher incidence of diffuse CAS and ECG changes in DES-CAS group shown in [Tables 1 and 2](#) and [3](#).

During the Ach provocation test, significant vasoconstriction response to Ach lower dose, mean narrowing diameter, diameter %, the incidence of baseline spasm, multi-vessel spasm and spasm location from proximal to distal are similar between the two groups ([Table 3](#)). However, the incidence of diffuse spasm (>20 mm) and ST-T change during the Ach provocation test was higher in the DES-CAS group ([Table 3](#)).

During 3-year follow-up there was no significant difference between the two groups, DES-CAS and CAS groups, regarding total death, cardiac death, MI, and CVA both before and after PSM (*p* value = NS) as shown in [Table 4](#). There was higher incidence of PCI in DES-CAS as compared to the CAS group both before and after PSM during follow-up and shown in [Table 4](#).

Table 1
Baseline clinical characteristics.

Variable. N (%)	Entire Patients				Propensity Score-Matched Patients			
	Total (n = 1986)	Stented-CAS (n = 108)	CAS (n = 1878)	p Value	Total (n = 204)	Stented-CAS (n = 102)	CAS (n = 102)	p Value
Gender (Male)	1042(52.4)	78 (72.2)	964(51.3)	<0.001	140(68.6)	73(71.5)	67(65.6)	0.365
Age	56.0 ± 11.3	60.6 ± 8.62	55.7 ± 11.5	<0.001	60.6 ± 8.9	60.4 ± 8.7	60.9 ± 9.1	0.714
Body mass index	24.3 ± 3.2	24.7 ± 3.1	24.3 ± 3.2	0.248	24.7 ± 3.0	24.7 ± 3.1	24.8 ± 2.9	0.814
Mean systolic BP	135 ± 22	129 ± 22	135 ± 22	0.005	130 ± 21	130 ± 22	130 ± 20	0.818
Mean diastolic BP	79 ± 13	76 ± 13	79 ± 13	0.010	76 ± 13	76 ± 13	76 ± 13	0.847
Heart rate	70 ± 12	67 ± 12	70 ± 12	0.020	67 ± 11	67 ± 12	67 ± 11	0.823
Pulse pressure	55 ± 16	52 ± 15	55 ± 16	0.098	53 ± 15	53 ± 15	54 ± 15	0.627
Hypertension	946(47.6)	72 (66.6)	874(46.5)	<0.001	133(65.1)	67(65.6)	66(64.7)	0.883
Diabetes	264 (13.2)	27 (25)	237(12.6)	<0.001	52 (25.4)	24(23.5)	28(27.4)	0.520
Dyslipidemia	383 (19.2)	28 (25.9)	355(18.9)	0.072	52 (25.4)	25(24.5)	27(26.4)	0.748
Stroke	70 (3.5)	12 (11.1)	58 (3.0)	<0.001	20 (9.8)	8 (7.8)	12(11.7)	0.346
Peripheral arterial disease	124 (6.2)	7 (6.4)	117 (6.2)	0.916	8 (3.9)	6 (5.8)	2 (1.9)	0.279
Smoking history	647 (32.5)	55 (50.9)	592(31.5)	<0.001	86 (42.1)	49(48.0)	37(36.2)	0.089
Current Smoker	490 (24.6)	40 (37)	450(23.9)	0.002	63 (30.8)	35(34.3)	28(27.4)	0.289
Alcoholic history	742 (37.3)	40 (37)	702(37.3)	0.943	76 (37.2)	38(37.2)	38(37.2)	Ns
Current alcoholic	645 (32.4)	31 (28.7)	614(32.6)	0.389	62 (30.3)	30(29.4)	32(31.3)	0.761

CAS, coronary artery spasm, BP, blood pressure.

Table 2
Baseline laboratory findings.

Variable. N (%)	Entire Patients				Propensity Score-Matched Patients			
	Total (n = 1986)	Stented-CAS (n = 108)	CAS (n = 1878)	p Value	Total (n = 204)	Stented-CAS (n = 102)	CAS (n = 102)	p Value
Creatinine	0.8 ± 0.3	0.9 ± 0.3	0.8 ± 0.4	<0.001	0.9 ± 0.2	0.9 ± 0.3	0.8 ± 0.2	<0.001
Total cholesterol	176 ± 41	145 ± 37	177 ± 41	<0.001	158 ± 38	145 ± 38	170 ± 39	<0.001
Triglyceride	132 ± 94	118 ± 87	133 ± 94	0.162	125 ± 90	117 ± 85	133 ± 95	0.256
LDL-C	111 ± 37	90. ± 36	112 ± 37	<0.001	98. ± 35	90. ± 36	105 ± 34	0.023
HDL-C	49 ± 13	43 ± 14	49 ± 13	<0.001	45 ± 13	43 ± 14	47 ± 12	0.041
Fasting Glucose	102 ± 24	105 ± 27	101 ± 24	0.248	105 ± 27	104 ± 26	106 ± 28	0.702
HbA1c	5.9 ± 0.8	6.2 ± 1.0	5.9 ± 0.8	0.009	6.2 ± 0.9	6.1 ± 0.9	6.3 ± 1.0	0.363
Hs-CRP	3.1 ± 11.1	5.4 ± 19.6	2.9 ± 10.6	0.288	5.0 ± 15.4	5.5 ± 20.3	4.3 ± 9.92	0.676
ESR	19.4 ± 21.8	20.5 ± 21.6	19.3 ± 21.8	0.679	20.4 ± 19.4	21.0 ± 22.0	19.3 ± 14.8	0.692
Fibrinogen	278 ± 109	264 ± 130	280 ± 107	0.293	278 ± 114	266 ± 131	301 ± 79.	0.196
Uric acid	4.9 ± 1.4	5.2 ± 1.3	4.8 ± 1.4	0.024	5.0 ± 1.4	5.2 ± 1.3	4.7 ± 1.4	0.062

LDL-C, low density lipoprotein. HDL-C, high density lipoprotein, HbA1c, glycated hemoglobin, ESR, erythrocyte sedimentation rate.

Similarly, there was higher incidence of recurrent angina requiring repeat CAG in DES-CAS in comparison to CAS group before PSM and this difference persisted after PSM shown in Table 4.

There were total 28 (1.4%) MACE during 3-year follow up before adjustment, 11(10.1%) in DES-CAS and 17(0.9%) in CAS group, this difference persisted after adjustment, total 11(5.3%) out which 10 (9.8%) were noted in DES-CAS, and 1 (0.9%) in CAS group shown in Table 4.

The Hazard ratio for MACE in DES-CAS in comparison to CAS group before PSM was 12.4, and this persisted significantly higher as 10.9 after adjustment with PSM, shown in Table 4.

4. Discussion

To our knowledge, this is the first study, comparing the clinical and angiographic outcomes of DES-associated CAS with native CAS in Asian population. In our study, the main findings were; 1) During Ach test, the incidence of diffuse spasm and ST-T change were higher in the DES-CAS group and 2) At 3-year, the DES-CAS group showed a higher incidence of coronary revascularization, recurrent chest pain requiring follow up coronary angiography and MACEs as compared to CAS group.

Higher MACE rate in our study is in line with other studies in which patients with CAS with underlying coronary artery lesion have an unfavorable prognosis as compared to those with isolated coronary artery spasm.¹⁴ Possible explanation for the higher

incidence of MACE in DES-CAS in our study may be that DES-CAS group has a higher burden of atherosclerosis, higher incidence of diffuse CAS, and dynamic ST-T ECG changes. Peter Ong and et al described a higher incidence of MACE in patients with CAS with underlying obstructive CAD as compared to those patients with CAS, but without obstructive CAD.¹⁴ Alternatively, MACE rate was only 0.9% in CAS group of the present, a findings corresponding to favorable outcomes in the former reports.¹⁴ Although, some reports have described a higher incidence of cardiac deaths and nonfatal myocardial infarction in subsets of patients with CAS but, without obstructive CAD.¹⁵ Bory et al reported 3.6% incidence of cardiac death and 6.5% of myocardial infarction during long term follow up of 277 French non-ACS patients, with CAS and non-obstructive CAD.¹⁶ However in our study no significant difference was observed between the two groups. And this may be due to relative lower number of smokers in our study (32.6%) as compared to Bory et al where 71.5% patient were smokers.¹⁶ Smoking is associated with constant and severe endothelial dysfunction and likely results in higher incidence of spasm associated myocardial infarction.^{17,18} Finally, in our study, recurrent angina requiring repeat CAG was 10 (9.8%) in DES-CAS and none in CAS only group after a PSM. This is different from other studies in which the repeat CAG for chest pain was 4% and 21% in patients with Ach negative test respectively.^{14,19} This difference might because other cause of chest pain, with normal coronary artery, is an abnormal coronary vaso reactivity of the coronary microcirculation. In these patients, there is an abnormality in the coronary microcirculation that lead to diminished

Table 3
Angiographic results and ECG changes during acetylcholine provocation test.

Entire Patients					Propensity Score-Matched Patients			
Variable. N (%)	Total (n = 1986)	Stented-CAS (n = 108)	CAS (n = 1878)	p Value	Total (n = 204)	Stented-CAS (n = 102)	CAS (n = 102)	p Value
Acetylcholine dose								
A1 (20 µg)	113 (5.6)	11 (10.2)	102 (5.4)	0.035	15 (7.3)	10 (9.9)	5 (4.9)	0.173
A2 (50 µg)	709 (35.7)	47 (43.9)	662 (35.2)	0.069	83 (40.8)	44 (43.5)	39 (38.2)	0.440
A3 (100 µg)	1163 (58.5)	49 (45.7)	1114 (59.3)	0.006	105 (51.7)	47 (46.5)	58 (56.8)	0.141
Reference diameter, mm(after NTG)								
	2.4 ± 0.7	2.3 ± 0.5	2.4 ± 0.8	0.159	2.3 ± 0.5	2.3 ± 0.5	2.4 ± 0.5	0.146
Narrowing diameter, mm (after Ach)								
	0.7 ± 0.3	0.7 ± 0.4	0.7 ± 0.3	0.741	0.7 ± 0.3	0.7 ± 0.4	0.7 ± 0.3	0.794
Narrowing diameter,% (after Ach)								
	70.3 ± 13.5	69.2 ± 15.3	70.3 ± 13.4	0.386	70.7 ± 14.0	69.7 ± 15.1	71.7 ± 12.9	0.321
Baseline spasm (narrowing≥30%)								
	527(26.5)	17 (15.7)	510(27.1)	0.009	31(15.1)	17(16.6)	14(13.7)	0.558
Myocardial bridge								
	657(33.0)	56 (51.8)	601 (32)	<0.001	92 (45)	52(50.9)	40(39.2)	0.091
Multi-vessel spasm								
	716(36.0)	52 (48.1)	664(35.3)	0.007	90(44.1)	49(48.0)	41(40.1)	0.259
Diffuse (≥20 mm)								
	1667 (83.9)	100 (92.5)	1567 (83.4)	0.012	178 (87.2)	95 (93.1)	83 (81.3)	0.012
ST-T segment change								
STD	133 (6.6)	14 (12.9)	119 (6.3)	0.007	13 (6.3)	11 (10.7)	2 (1.9)	0.010
STE	58 (2.9)	9 (8.3)	49 (2.6)	0.003	9 (4.4)	7 (6.8)	2 (1.9)	0.170
T-inversion	51 (2.5)	5 (4.6)	46 (2.4)	0.196	4 (1.9)	4 (3.9)	0 (0.0)	0.121
AV block	24 (1.2)	0 (0.0)	24 (1.2)	0.638				
AV block	360 (18.1)	27 (25)	333 (17.7)	0.057	50 (24.5)	25 (24.5)	25 (24.5)	ns
Spasm site								
Left Main	6 (0.3)	0 (0.0)	6 (0.3)	Ns				
LAD	1180 (59.4)	55 (50.9)	1125 (59.9)	0.065	111 (54.4)	53 (51.9)	58 (56.8)	0.482
LCX	79 (3.9)	1 (0.9)	78 (4.1)	0.125	3 (1.4)	0 (0.0)	3 (2.9)	0.246
Left coronary artery; (LAD + LCX)	700 (35.2)	52 (48.1)	648 (34.5)	0.004	89 (43.6)	49 (48.0)	40 (39.2)	0.204
Proximal to distal								
	832 (41.8)	46 (42.5)	786 (41.8)	0.880	81 (39.7)	43 (42.1)	38 (37.2)	0.474
Mid to distal								
	731 (36.8)	50 (46.2)	681 (36.2)	0.036	88 (43.1)	48 (47.0)	40 (39.2)	0.258
Proximal								
	136 (6.8)	3 (2.7)	133 (7.0)	0.085	10 (4.9)	2 (1.9)	8 (7.8)	0.052
Mid								
	254 (12.7)	7 (6.4)	247 (13.1)	0.044	20 (9.8)	7 (6.8)	13 (12.7)	0.158
Distal								
	33 (1.6)	2 (1.8)	31 (1.6)	0.700	5 (2.4)	2 (1.9)	3 (2.9)	Ns

A1,A2, A3 Acetylcholine doses, Ach, Acetylcholine, STD, ST segment depression, STE, ST segment elevation, LAD, left anterior descending artery, LCX, left circumflex artery, AV block, atrioventricular block.

Table 4
Three-year cumulative clinical outcomes.

Entire Patients					Propensity Score-Matched Patients			
3-year outcome	Total (n = 1986)	DES-CAS (n = 108)	CAS (n = 1878)	p Value	Total (n = 204)	DES-CAS (n = 102)	CAS (n = 102)	p Value
Mortality	7 (0.3)	2 (1.8)	5 (0.2)	0.051	2 (0.9)	1 (0.9)	1 (0.9)	ns
Cardiac death	5 (0.2)	1 (0.9)	4 (0.2)	0.244	1 (0.4)	1 (0.9)	0 (0.0)	ns
Myocardial infarction; MI	8 (0.4)	2 (1.8)	6 (0.3)	0.066	2 (0.9)	2 (1.9)	0 (0.0)	0.498
PCI	19 (0.9)	10 (9.2)	9 (0.4)	<0.001	10 (4.9)	10 (9.8)	0 (0.0)	0.001
Cerebrovascular accidents; CVA	5 (0.2)	1 (0.9)	4 (0.2)	0.244	1 (0.4)	0 (0.0)	1 (0.9)	ns
Repeat CAG ^a	194 (9.7)	27 (25.0)	167 (8.8)	<0.001	33 (16.1)	25 (24.5)	8 (7.8)	0.001
MACE; Mortality, PCI, MI	28 (1.4)	11 (10.1)	17 (0.9)	<0.001	11 (5.3)	10 (9.8)	1 (0.9)	0.005
	HR:12.4 (95%CI: 5.66–27.2)			<0.001	HR: 10.9 (95%CI: 1.37–87.4)			0.024

DES-CAS, drug eluting stent coronary artery spasm, CAS, coronary artery spasm, MI; myocardial infarction, PCI; percutaneous coronary intervention, CAG; coronary angiography, MACE, major adverse cardiovascular events.

^a Repeat CAG; Recurrent angina requiring follow up angiography.

coronary reserve or microvascular spasm²⁰ resulting repetitive angina during rest or exercise.²¹

4.1. Clinical implications

Patients with CAS without obstructive CAD has good long-term outcome, but DES-associated CAS spasm is associated with more diffuse spasm, dynamic ST-T change, higher incidence of long-term recurrent angina requiring repeat CAG, PCI and MACE, thus needs close and more frequent follow up with optimal medical therapy.

4.2. Study limitation

First, Ach provocation test was not done in DES-CAS groups during index stenting procedure period and could not be stated with certainty that DES was responsible for CAS and unfavourable clinical outcomes in this group. However, DES, especially the first-generation DES, is proven to be the recognized as a major cause of

significant endothelial dysfunction and subsequent significant CAS. Second limitation in our study, is that we have not analyzed our data according to stents types because spasm is more commonly reported with first generation DES, but most patients in our study were implanted first generation DES. This is an observation study and variable were matched through PSM, and can leads to hypothesis generation, and need more evidences through a randomized trial.

4.3. Conclusion

In this study, DES-associated CAS was associated with more diffuse spasm, dynamic ST-T change, higher incidence of long-term recurrent angina requiring repeat CAG, PCI and MACE. Special caution should be exercised in this particular subset of patients. DES associated coronary spasm is associated with adverse clinical outcomes and future studies on a larger scale and population are needed.

Declaration of competing interest

Nil.

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