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

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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) and 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. 9.8%, 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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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 results in different biological responses and eventually impact on net clinical outcomes.1–13 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.14–16 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.17–19 Whereas in one study relatively preserved endothelial dependent vasomotor function was shown 9 months after biolimus-eluting stents implantation.19 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 define 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-Meir 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 were 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.
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 (9.9%) 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. 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. Alternatively, MACE rate was only 0.9% in CAS group of the present, a findings corresponding to favorable outcomes in the former reports. 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. 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. 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. Smoking is associated with constant and severe endothelial dysfunction and likely results in higher incidence of spasm associated myocardial infarction. 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 significantly lower number of smokers in our study (32.6%) as compared to Bory et al where 71.5% patient were smokers. Smoking is associated with constant and severe endothelial dysfunction and likely results in higher incidence of spasm associated myocardial infarction. In these patients, there is an abnormality in the coronary microcirculation that lead to diminished normality in the coronary microcirculation that lead to diminished normal coronary artery, is an abnormal coronary vaso reactivity of normal 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. Alternatively, MACE rate was only 0.9% in CAS group of the present, a findings corresponding to favorable outcomes in the former reports. 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. 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. 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. Smoking is associated with constant and severe endothelial dysfunction and likely results in higher incidence of spasm associated myocardial infarction. 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. 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 normality in the coronary microcirculation that lead to diminished normal coronary artery, is an abnormal coronary vaso reactivity of normal coronary artery spasm. 14
coronary reserve or microvascular spasm resulting repetitive angina during rest or exercise.\textsuperscript{21}

### 4.1. Clinical implications

Patients with CAS without obstructive CAD has good long-term outcome, but DES-associated CAS 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 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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