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Original article

The real-world prevalence of cardiovascular events related to coronary spasm after percutaneous coronary intervention☆

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ABSTRACT

Background: It is unknown to what extent coronary spasm affects cardiovascular events after percutaneous coronary intervention (PCI) in clinical practice. The aim was to examine the prevalence of cardiovascular events related to coronary spasm following PCI according to stent type.
Methods: We enrolled 933 consecutive patients treated with coronary stent implantation, including bare metal stents (BMS; $n = 238$), first-generation drug-eluting stents (*1st* DES; $n = 185$), and second-generation DES (*2nd* DES; $n = 510$). We compared stent-oriented endpoints (SOEs; stent thrombosis, target vessel myocardial infarction or unstable angina, target lesion revascularization, and cardiac death) and the differences in SOE related to coronary spasm across stent types. Among the SOEs, spasm-related cardiac event was defined based on JCS guideline.
Results: The prevalence of SOE for each stent type was 16.8% (BMS), 16.8% (*1st* DES), and 7.8% (*2nd* DES) ($p < 0.001$) and the rates of cardiovascular events related to coronary spasm were 2.9%, 3.2%, and 0.4%, respectively ($p = 0.005$). Multivariate analysis identified the non-use of statin (HR, 0.275, 95% CI, 0.087–0.871, $p = 0.028$) and non-use of *2nd* DES (hazard ratio, 0.196, 95% confidence interval, 0.043–0.887, $p = 0.034$) as independent predictors of cardiac events related to coronary spasm.
Conclusion: The prevalence of cardiovascular events related to coronary spasm was the lowest in patients with *2nd* DES. The *2nd* DES may be more efficacious and safer from the point of view of the reduction of cardiac events due to coronary spasm during statin therapy.

Introduction

Percutaneous coronary intervention (PCI) with stenting is widely used for the treatment of coronary artery disease (CAD) [1]. First-generation drug-eluting stents (*1st* DES) such as the sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) significantly reduce the risk of target vessel revascularization compared to bare-metal stents (BMS) [2]. However, concern has been raised over the propensity for late or very late stent thrombosis with *1st* DES, which has frequent, life-threatening consequences and requires prolonged dual antiplatelet therapy [3–5]. To overcome these issues, second-generation DESs (*2nd* DES) have been developed, with advanced design features, more biocompatible or bioresorbable polymers, and more effective drugs. These have been shown to improve clinical outcomes over *1st* DES [6–8].

The *1st* DES has also been associated with endothelial dysfunction and coronary vasoconstriction, compared to BMS [9–11]. One manifestation of coronary endothelial dysfunction is coronary spasm, characterized by transient total or subtotal occlusion or severe diffuse vasoconstriction of an epicardial artery. Coronary spasm is an important contributor to the pathogenesis of CAD [12–15]. Coronary spasm is prevalent among Japanese patients with CAD and is often asymptomatic in patients with coronary spastic angina [12–14]. Although we have reported a high incidence of acetylcholine (ACh)-induced coronary spasm after *2nd* DES or BMS implantation, this is a provocation test, rather than testing spontaneous coronary spasm, and the tested phenomenon

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is not often found in daily clinical practice [16]. Thus, it is unknown to what extent coronary spasm affects cardiovascular events after PCI in clinical practice. In the present study, we compared the incidence of cardiovascular events due to coronary spasm after stenting with a BMS, *1st* DES, or *2nd* DES in daily clinical practice. We also examined predictive factors for coronary spasm-related cardiovascular events.

Methods

Study subjects

We consecutively enrolled CAD patients who underwent coronary stent implantation from January 2007 to November 2014 in Kumamoto University Hospital, and followed them prospectively. The patients received DES as a default strategy, except for cases with several clinical situations. The decision to select BMS was made based on the presence of conditions such as ST-elevation myocardial infarction, high bleeding risk, active malignant disease, anticipated major surgery, or the discretion of the treating physician. In the era of *2nd* DES, *2nd* DESs were used in clinical practice instead of *1st* DES. Exclusion criteria included cases treated with both BMS and DES in the same patient, cases with in-hospital death, and cardiovascular events during hospitalization for the first PCI. Ultimately, the study comprised 933 consecutive patients (664 males and 269 females, mean age 70.0 ± 10.3 years), with BMS (n = 238), *1st* DES (n = 185) [SES (Cypher®, Cordis, Johnson & Johnson, Warren, NJ, USA) and PES (Taxus®, Boston Scientific, Marlborough, MA, USA)] and *2nd* DES (n = 510) [cobalt-chromium everolimus-eluting stent (CoCr-EES, Xience®, Abbott Vascular, Santa Clara, CA, USA), biolimus-eluting stent (BES, Nobori®, Terumo Corporation, Tokyo, Japan), platinum-chromium everolimus-eluting stent (PtCr-EES, PROMUS® stent, Boston Scientific), and zotarolimus-eluting stent (ZES, Resolute®, Medtronic Inc, Santa Rosa, CA, USA)]. Fig. 1 shows the flow diagram of this study.

Coronary stent implantation was performed according to the guidelines for PCI [1,17,18]. The risk factors assessed included hypertension, history of smoking, plasma levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, high-density lipoprotein (HDL)-cholesterol, glucose, type 2 diabetes mellitus, uric acid, body mass index, and previous history of cardiovascular disease. The study was conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was in agreement with the guidelines of the ethical committee of Kumamoto University and was approved by the Institutional Review Board of Kumamoto University. Written informed consent was obtained from each patient or the family of the subject.

Dual antiplatelet therapy (DAPT) was continued for 1 year in acute coronary syndrome (ACS) patients irrespective of BMS or DES. In cases with stenting in left main trunk or two stents in bifurcation lesions, DAPT was continued over 1 year, if hemorrhagic risk was low. Other medication was performed according to guidelines at that time.

Blood pressure was assessed before PCI, and presence of hypertension was defined as a systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or the use of antihypertensive medication.

Clinical outcomes

Stent-oriented endpoint (SOE) was defined as a composite of stent thrombosis, target vessel-related non-fatal myocardial infarction or unstable angina requiring hospitalization, ischemia-driven target lesion revascularization, and cardiac death. Although it is unknown whether cardiac death is directly due to the stented segment failure, as previously reported, we included cardiac death as a SOE [19]. Stent thrombosis, defined by the Academic Research Consortium criteria, was also analyzed separately. Subjects were followed up every month as outpatients if possible. For patients referred to another hospital, cardiovascular events were surveyed by telephone calls to the subjects or their families, followed by a review of the medical records of the referred hospitals. All patients were followed up during study.

Moreover, we performed coronary angiogram (CAG) for a patient with recurrence of angina attack after PCI, and even in patients without overt chest symptoms, follow-up CAG or coronary computed tomography angiogram is routinely performed from 6 to 12 months after stenting. Revascularization is performed in symptomatic patients based on the proof of myocardial ischemia using exercise test or scintigraphy.

Cardiovascular death was defined as death due to myocardial infarction, congestive heart failure that could be attributed to the failure of the implanted stent vessel, or documented sudden cardiac death. We used the universal definition of myocardial infarction in this study [20]. To avoid overlap of the number of cardiac events in this study, in a case of acute myocardial infarction due to stent thrombosis according to the Academic Research

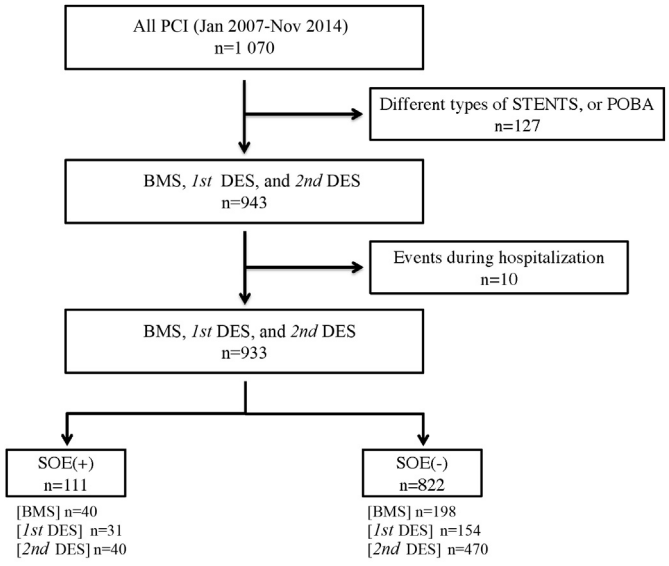

Fig. 1. Flow diagram of cardiac events after stent implantation. BMS, bare-metal stent; *1st* DES, first-generation drug-eluting stent; *2nd* DES, second-generation drug-eluting stent; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; SOE, stent-oriented cardiac event.

Table 1
Criteria for the clinical diagnosis of cardiovascular events related to coronary spasm.

Criteria elements
1) Nitrate-responsive typical chest pain during angina attack
2) Transient ischemic ST changes during angina attack, including any of the following in at least two contiguous leads on electrocardiogram (ECG)
[a] ST-segment elevation ≧0.1 mV
[b] ST-segment depression ≧0.1 mV
[c] New negative U waves
3) Coronary artery spasm – defined as transient total or subtotal coronary artery occlusion (>90% constriction) with a typical chest pain and ischemic ECG changes either spontaneously or in response to a provocation stimulus (acetylcholine or ergonovine)
Exclusion criteria
1) Coronary angiogram or coronary computed tomography angiogram does not show severe stenosis in both stented site and non-stented site, or coronary thrombus
2) There are no secondary factors including anemia, fever, or hyperthyroid