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Comparison of Endothelial Dysfunction in Coronary Arteries with Bare Metal and 2nd-Generation Drug-Eluting Stents

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Aims: Previous studies suggested that implantation with a 1st-generation DES was associated with coronary endothelial dysfunction, which was associated with Rho-kinase activation. Second-generation drug-eluting stents (DESs) may preserve coronary endothelial function in stented coronary arteries; however, because of methodological limitations, further study is needed to clarify the association between 2nd-generation DESs and coronary endothelial dysfunction.

Methods: We retrospectively analysed the CuVIC trial database, where we identified 112 patients who underwent coronary stenting in the left coronary arteries with either a bare metal stent (BMS, $n=53$) or 2nd-generation DES ($n=59$). We compared vasomotions of target vessels with stents and non-target vessels without stents. Furthermore, we measured the Rho-kinase activation detected in mononucleocytes from aortic and coronary sinus blood.

Results: ACh-induced vasoconstrictive responses of target vessels were not enhanced with a 2nd-generation DES (45 ± 21% vs. 44 ± 20%, $P=0.56$, paired t-test), but significantly enhanced in the coronary arteries with a BMS (50 ± 18% vs. 42 ± 20%, $P=0.002$). Rho-kinase activation did not differ between patients with a BMS and 2nd-generation DES. In the target vessels with a BMS, large late lumen loss and acute coronary syndrome (ACS) at the index percutaneous coronary intervention (PCI) were associated with ACh-induced enhanced coronary vasoconstrictive responses.

Conclusions: Evaluation of ACh-induced vasomotion of target vessels comparing with non-target vessels revealed that 2nd-generation DESs were not associated with coronary endothelial dysfunction in target vessels, nor activation of Rho-kinase in the coronary sinus blood 6-8 months after stenting.

Key words: Coronary endothelial dysfunction, 2nd-generation drug-eluting stent, Bare metal stent, Percutaneous coronary intervention, Late lumen loss

Abbreviations: ACh, acetylcholine; BMS, bare metal stent; DES, drug-eluting stent; PCI, percutaneous coronary intervention; LCA, left coronary artery; ACS, acute coronary syndrome

Introduction

Coronary endothelial dysfunction precedes atherogenesis and plays an important role in the progression of atherosclerosis and coronary artery disease, which requires coronary revascularization, such as coronary stenting[1, 2]. In clinical studies, coronary endothelial dysfunction is defined as an impairment of vasodilation in response to intracoronary acetylcholine (ACh), and it has been shown to independently predict future cardiovascular events in prospective studies[3-5]. The development of

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drug-eluting stents (DESs) has provided efficacious therapeutic options for coronary revascularization in coronary artery disease by localized elution of antiproliferative drugs to inhibit neointima formation and thereby reduce in-stent restenosis compared with bare metal stents (BMSs)[6-9]. However, several studies have raised concerns that 1st-generation DESs were associated with delayed or incomplete re-endothelialization, leading to a higher risk of late stent thrombosis[10, 11]. It was suggested from case studies that coronary endothelial dysfunction in coronary arteries stented with 1st-generation DES might cause coronary events in the late phase[12, 13]. Recently, it was shown that a 2nd-generation DES may reduce the adverse effects of the 1st-generation DESs, such as stent thrombosis, with better long-term clinical performance, including a lower risk of myocardial infarction[14]. These notions imply that better coronary endothelial function might underpin better clinical outcomes after the implantation of 2nd-generation DESs. However, the assessment of coronary endothelial function in previous studies was limited because they compared coronary vasoreactivity between patient groups with different stents that are placed without randomization, which might introduce significant selection biases. This selection bias can be overcome by comparing the vasoreactivity between stented target vessels and nonstented non-target vessels as an internal control in each patient.

Coronary endothelial dysfunction results from a reduction in endothelial nitric oxide bioavailability and hypercontraction of VSMCs, which are difficult to assess in clinical studies[15]. Recently, phosphorylation of the myosin-binding subunit of myosin light-chain phosphatase, a substrate of Rho-kinase, was measured as Rho-kinase activity in peripheral mononuclear cells[16]. Increased Rho-kinase activity in peripheral mononuclear cells have been shown to be associated with metabolic syndrome[17] and endothelial dysfunction[18], which may be useful for interpreting the mechanisms of coronary endothelial dysfunction associated with coronary stents.

Aim

In this study, we retrospectively analyzed coronary responses to ACh in both target vessels and non-target vessels as an internal control in either the left anterior descending artery (LAD) or left circumflex artery (LCx) and Rho-kinase activity in the coronary circulation 6-8 months after stenting. We aimed to examine our hypothesis that vasoconstrictive responses in target vessels after 2nd-generation DES implantation are not different from those in non-target vessels, and to explore potential mechanisms that affect coronary endothelial function in stented target vessels.

Methods and Population

Study Population

The CuVIC trial, a prospective randomized trial that we conducted from June 2011 to September 2013, tested the effects of lipid-lowering therapy with statins and ezetimibe on coronary endothelial dysfunction, as described previously[19]. All patients signed a written informed consent prior to enrollment, and local institutional review boards approved the study. In brief, patients with coronary artery disease who underwent coronary stenting with a BMS (n=129, 50%) or 2nd-generation DES (n=129, 50%) were randomized to receive statin monotherapy or ezetimibe and statin combinational therapy with stratification by stent type. After 6-8 months, patients were subjected to coronary angiography, and patients without restenosis or de novo lesions underwent intracoronary ACh testing to evaluate coronary vascular responses[19]. In this subanalysis, we assessed the eligibility of 258 Japanese patients in the CuVIC trial database full analysis set. **(Fig. 1)**. In this study, the patients with target vessel failures (TVFs), a composite of target vessel-related death, myocardial infarction, and ischemia-driven target vessel revascularization were excluded. The incidences of TVFs at follow-up was 36 (19 in the BMS group and 17 in the 2nd-generation DES group, respectively). The patients' characteristics of the BMS group and the 2nd-generation DES group were comparable except for baseline heart rate and the usage of insulin, as shown in the **supplementary Table 1, 2**. In addition, baseline patients' characteristics of the 36 patients with TVF were compared with those of the 112 patients who had been performed ACh testing without TVFs, as shown in the **supplementary Table 3, 4**. The patients' characteristics between 2 groups were almost similar, except for the prevalence of hypertension and family history of ischemic heart disease. We identified 112 patients who underwent intracoronary ACh testing in the LCA and stenting with a BMS (n=53) or 2nd-generation DES (n=59) in the target coronary arteries.

Intracoronary ACh Tests and Coronary Endothelial Dysfunction

All patients underwent coronary angiography and ACh tests at least 48 hours after cessation of coronary dilators, such as calcium channel blockers

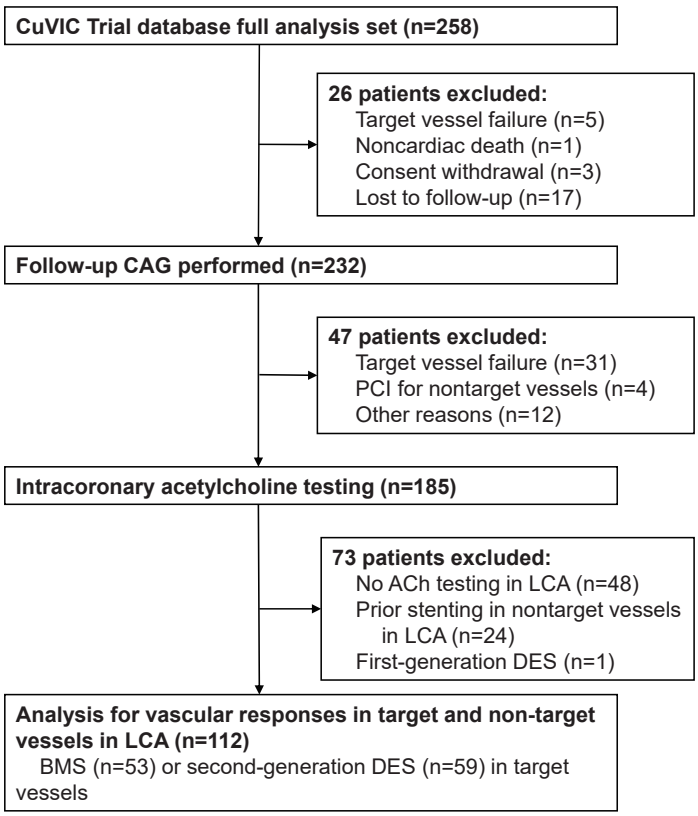

Fig. 1. Study flow

Among 258 patients in the CuVIC trial database, 112 patients who underwent stenting in left coronary arteries (BMS, $n=53$ and DES, $n=59$) and intracoronary ACh testing were analyzed in this study.
CAG, coronary angiography, PCI, percutaneous coronary intervention, ACh, acetylcholine, RCA, right coronary artery.

(CCBs) or nitrates. Baseline coronary angiography followed the administration of incremental doses of ACh (10 μg, 30 μg, and 100 μg) into the left coronary artery until the diagnostic criteria for coronary endothelial dysfunction were met. This was followed by an isosorbide dinitrate (ISDN) injection to obtain a reference diameter.

Coronary responses were assessed with quantitative coronary angiography (QCA) software (PIE Medical Imaging, Maastricht, Netherlands) by independent observers blinded to the study protocol at the Data Center of Clinical and Translational Research, Kyushu University. Coronary responses to ACh in target vessels and non-target vessels were measured by QCA during end-diastole accordingly. In the non-target vessel, coronary luminal diameter was measured at the most vasoactive coronary segment at baseline, at 60 seconds after the injection of incremental doses of intracoronary ACh (A), and after ISDN injection to determine reference diameter (R). Vasoconstriction was determined as a percentage of maximal luminal narrowing during ACh injections.

Vasoconstriction (%) = (R − A)/R × 100

In the target vessels, similar measurements were performed at the distal segments of the stents.

Measurement of Late Lumen Loss

We determined the minimum lumen diameter (MLD) of the target lesion, which was defined as the index stent site including 5 mm proximal and distal to the stent based on coronary angiography after intracoronary ISDN injection. The in-stent stenosis ratio and late lumen loss were determined as follows.

In-stent diameter stenosis (%) = (R − MLD)/R × 100

Late lumen loss (mm) = R − MLD

The Assay for Rho-kinase (ROCK) Activity

Mononuclear cells were isolated from 15 mL blood samples drawn from the aorta and coronary sinus (CS) during cardiac catheterization following a

Table 1. Baseline Clinical Characteristics

	Total ($n=112$)	BMS ($n=53$)	2nd-Gen DES ($n=59$)	p-value
Demographics				
Age (years)	66 ± 10	64 ± 11	67 ± 9	0.095
Male, *n* (%)	86 (77)	46 (87)	40 (68)	0.024
Body mass index (kg/m^2)	25 ± 4	25 ± 4	25 ± 4	0.74
Heart rate (bpm)	67 ± 9	70 ± 11	69 ± 11	0.81
Systolic blood pressure (mmHg)	123 ± 16	121 ± 16	124 ± 16	0.26
Left ventricular ejection fraction (%)	65 ± 10	64 ± 11	67 ± 9	0.10
Risk factors, *n* (%)				
Hypertension	69 (62)	26 (49)	43 (73)	0.0012
Diabetes mellitus	53 (47)	22 (42)	31 (53)	0.26
Dyslipidemia	103 (92)	48 (91)	55 (93)	0.73
Smoking	38 (35)	23 (44)	15 (26)	0.048
Family history	23 (21)	12 (23)	11 (19)	0.65
Medical treatment, *n* (%)				
Aspirin	112 (100)	53 (100)	59 (100)	-
$P2Y_{12}$ inhibitor	111 (99)	52 (98)	59 (100)	0.47
Other antiplatelet	3 (3)	2 (4)	1 (2)	0.60
Anticoagulant	11 (10)	9 (17)	2 (3)	0.024
ARB	34 (30)	14 (26)	20 (34)	0.42
ACE Inhibitor	30 (27)	17 (32)	13 (22)	0.29
β-Blocker	62 (55)	27 (51)	35 (59)	0.45
CCB	48 (43)	17 (32)	31 (53)	0.036
Nitrate	18 (16)	9 (17)	9 (15)	1
Statin	112 (100)	53 (100)	59 (100)	-
Ezetimibe	62 (55)	26 (49)	36 (61)	0.25
Antidiabetic agents	40 (35)	14 (26)	26 (44)	0.075
Insulin	13 (12)	6 (11)	7 (12)	1
Laboratory tests				
Total cholesterol (mg/dL)	148 ± 29	149 ± 31	147 ± 26	0.82
HDL cholesterol (mg/dL)	49 ± 13	49 ± 13	49 ± 13	0.76
LDL cholesterol (mg/dL)	73 ± 25	75 ± 28	72 ± 23	0.52
Triglyceride (mg/dL)	128 ± 65	125 ± 55	130 ± 73	0.72
Creatinine (mg/dL)	0.8 ± 0.3	0.9 ± 0.2	0.8 ± 0.3	0.65
HbA1c (%)	6.3 ± 1.2	6.2 ± 1.2	6.5 ± 1.2	0.16

Variables are *n* (%) or mean ± S.D.
Abbreviations: BMS: bare metal stent, DES: drug-eluting stent, ARB: angiotensin II receptor blocker, ACE: angiotensin-converting enzyme, CCB: calcium channel blocker, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HbA1c: hemoglobin A1c.

standardized protocol in 69 patients for whom CS cannulation was possible[17]. Briefly, the mononucleocytes were isolated from the blood sample by centrifuging with an equal volume of Histopaque-1077 (Sigma-Aldrich Co., St. Louis, MO). The mononuclear cells were collected, and protein samples were subjected to western blotting for the phosphorylated myosin binding subunit (p-MBS) of myosin light-chain phosphatase with an antibody for phosphorylated MYPT1 (Thr853) (Millipore, Billerica, MA) and total MBS (t-MBS) with an antibody for MYPT1 (BD Biosciences, Franklin Lakes, NJ) in the mononucleocyte samples from the coronary sinus and aorta. The ratio of MBS phosphorylation levels (p-MBS/t-MBS)^{CS} / (p-MBS/t-MBS)^{aorta} was defined as Rho-kinase activation in the coronary circulation[17].

Statistical Analysis

Statistical analyses were performed using JMP software (version 14.0.0, SAS Institute Inc., Cary, NC). Continuous variables are reported as the means ± SDs. For continuous variables, Student's *t*-test was used to test for differences between groups. Categorical variables were assessed with the Chi-square test or Fisher's exact probability test when

Table 2. Angiographical findings at the index PCI and follow-up CAG

	Total ($n=112$)	BMS ($n=53$)	2nd-Gen DES ($n=59$)	p-value
Index PCI				
Target vessel, n (%)				
LAD	90 (80)	41 (77)	49 (83)	0.48
LCx	22 (20)	12 (23)	10 (17)	0.48
Acute coronary syndrome, n (%)	44 (39)	24 (45)	20 (34)	0.25
Stent diameter (mm)	3.2 ± 0.5	3.3 ± 0.5	3.0 ± 0.4	< 0.001
Stent length (mm)	20 ± 7	18.8 ± 5.9	21.1 ± 7.6	0.075
DES type, n (%)				
Everolimus-eluting stent		-	41 (69)	
Zotarolimus-eluting stent		-	9 (15)	
Biodegradable polymer Biolimus-eluting stent		-	9 (15)	
Follow-up CAG				
Reference vessel diameter (mm)	2.7 ± 0.6	2.7 ± 0.6	2.7 ± 0.6	0.10
In-stent minimum lumen diameter (mm)	2.1 ± 0.5	2.0 ± 0.5	2.2 ± 0.5	0.0077
In-stent diameter stenosis (%)	21 ± 13	27 ± 14	17 ± 10	< 0.001
Late lumen loss (mm)	0.59 ± 0.40	0.73 ± 0.43	0.46 ± 0.30	< 0.001

Variables are n (%) or mean ± S.D.
Abbreviations: BMS: bare metal stent, DES: drug-eluting stent, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, LCx: left circumflex artery, CAG: coronary angiography

appropriate. A comparison of the vasoconstriction between stented target vessels and non-target vessels in the groups with different types of stents was analyzed by a paired t-test. A p-value <0.05 was considered statistically significant.

Results

Clinical Characteristics

A total of 112 subjects who had undergone coronary stenting in the left coronary artery were included from the CuVIC trial database **(Fig. 1)**. **Table 1** summarizes the clinical and angiographic characteristics of subjects with a BMS ($n=53$) or 2nd-generation DES ($n=59$). Stent types were selected by the physician at the index PCI before enrollment into the CuVIC trial. There were no significant differences in age or comorbidities, such as diabetes mellitus, dyslipidemia, smoking history, or family history of ischemic heart disease, between the two groups. Clinical presentation at the index PCI such as acute coronary syndrome (ACS) or non-ACS and left ventricular ejection fraction (LVEF) were also comparable between the groups. Biomarkers such as LDL-cholesterol (LDL-C) were also comparable. The BMS group included more males, increased use of anticoagulant therapy and fewer hypertensive patients. Angiographical findings **(Table 2)** indicate that a BMS was used in lesions with larger vessel diameters at the index PCI but resulted in larger late lumen loss at the follow-up CAG.

Vasoconstrictive Responses to ACh in the Stented Target Vessels and Non-Target Vessels

We examined vasoconstrictive responses to intracoronary ACh in each stented coronary artery (target vessels) compared to native coronary arteries (non-target vessels) **(Fig. 2A)**. QCA measurements of coronary vasomotor responses to ACh among patients with a BMS or 2nd-generation DES are summarized in **Fig. 2B**. In patients with a BMS, constrictive responses to ACh were more pronounced in target vessels than in non-target vessels (50 ± 18% vs. 42 ± 20%, $P=0.002$, paired t-test). On the other hand, in patients with a 2nd-generation DES, those were comparable between the target vessel and non-target vessel. (45 ± 21% vs. 44 ± 20%, $P=0.56$).

Rho-Kinase Activity in Blood Mononuclear Cells

Previous studies suggested that implantation with a 1st-generation DES was associated with hypercontractility of the coronary artery, both in humans and animals, which was associated with Rho-kinase activation. Therefore, we examined the phosphorylation of MBS, namely, the ratio of phosphorylated MBS to total MBS, by ELISA in mononucleocytes in the aorta and CS as an indicator of Rho-kinase activation in the coronary circulation. The correlation between Rho-kinase activation and coronary vasoconstriction did not reach significance in this study **(Fig. 3A)**. However, Rho-kinase activity was comparable between patients with a BMS and those with a 2nd-generation DES (BMS 0.66 ± 0.72 vs.

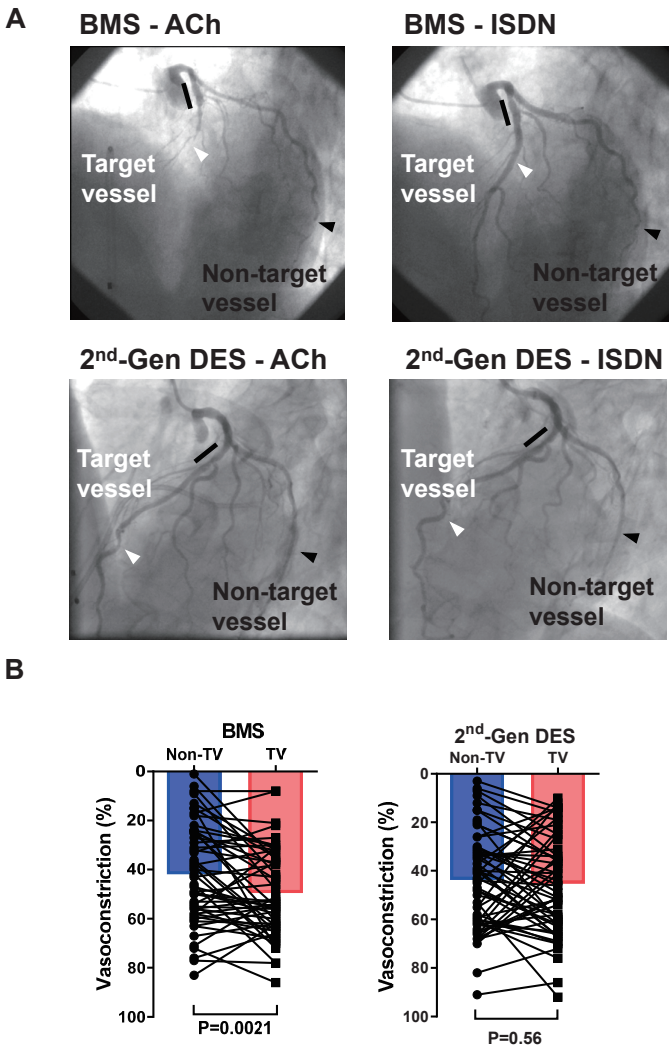

Fig. 2. Hyperconstrictive responses to intracoronary ACh in-stent target vessels and non-target vessels

A. Coronary angiograms (a) after intracoronary ACh with a BMS and (b) after intracoronary ISDN with a BMS, (c) after intracoronary ACh with a DES, and (d) after intracoronary ISDN with a DES. Upon stimulation by ACh, coronary artery spasm was induced at the distal segment of the coronary lesion implanted with a BMS but not with a 2nd-generation DES. The bar indicates a stent. The triangles indicate the points where the vessel diameter was measured.

B. Comparison of coronary vasoconstrictive responses to ACh between target vessels or non-target vessels among patients with a BMS ($n=53$) or 2nd-generation DES ($n=59$).

BMS, Bare metal stent; DES, drug-eluting stent; ACh, acetylcholine; ISDN, isosorbide dinitrate

DES 0.52±0.74, $P=0.42$ by t-test), suggesting that enhancing coronary vasoconstrictive responses in the target vessel compared to the non-target vessel in patients with a BMS were caused through mechanisms other than Rho-kinase activation **(Fig. 3B)**.

Clinical and Angiographic Factors Associated with Coronary Endothelial Dysfunction after Stenting

To seek insights into the enhanced vasoconstriction in the target coronary arteries with a BMS, we assessed clinical factors associated with ACh-induced hyperconstriction in target vessels compared with non-target vessels (**Table 3**). Among clinical and angiographic factors, stent type (BMS), ACS at the index PCI, and large late lumen loss divided by the median value (0.49 mm) were associated with coronary hyperconstriction in target vessels compared with non-target vessels. When grouped by the type of stent, the proportions of ACS were similar (24/53 patients with a BMS and 20/59 patients with a

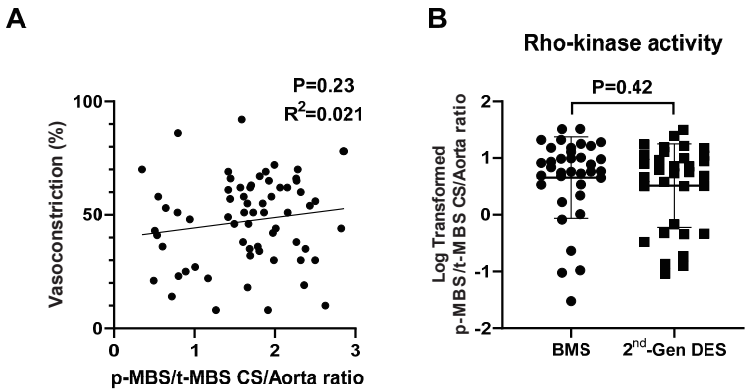

Fig. 3. Rho-kinase activity and vasoconstrictive responses

A. Correlation between Rho-kinase activation and vasoconstrictive responses to intracoronary ACh in stented coronary arteries.
B. Comparison of Rho-kinase activation between subjects with a BMS ($n=36$) and 2nd-generation DES ($n=33$). Variables of the Rho-kinase activation are log-transformed.
ACh, acetylcholine; BMS, bare metal stent; DES, drug-eluting stent

Table 3. Clinical and angiographic factors associated with ACh-induced vasoconstriction in the TV

		n (%)	Non-target vessel % vasoconstriction (mean ± SD)	Target vessel % vasoconstriction (mean ± SD)	*p*-value (paired *t*-test)
Demographics					
Sex	Male	86 (77)	44 ± 21	49 ± 20	0.08
	Female	26 (23)	40 ± 19	42 ± 18	0.54
Coronary lesion factors					
Stent type	BMS	53 (47)	42 ± 21	50 ± 18	0.0021
	2nd-Gen DES	59 (53)	44 ± 21	46 ± 21	0.56
ACS	+	44 (39)	42 ± 21	49 ± 19	0.017
	-	68 (61)	44 ± 20	46 ± 20	0.23
Late lumen loss	Large	57 (51)	43 ± 20	46 ± 21	0.04
	Small	55 (49)	43 ± 21	47 ± 19	0.09
Risk factors					
Hypertension	+	69 (61)	39 ± 20	44 ± 20	0.09
	-	43 (39)	50 ± 20	53 ± 18	0.27
Diabetes mellitus	+	53 (47)	43 ± 19	46 ± 19	0.22
	-	59 (53)	439 ± 22	49 ± 20	0.1
Dyslipidemia	+	103 (92)	43 ± 20	47 ± 19	0.09
	-	9 (8)	42 ± 28	48 ± 23	0.19
Smoking	+	38 (35)	47 ± 19	52 ± 18	0.09
	-	72 (65)	41 ± 21	45 ± 20	0.06

Abbreviations: BMS: bare metal stent, DES: drug-eluting stent, ACS: acute coronary syndrome

2nd-generation DES; $P=0.25$ by Fisher's exact test). ACS at the index PCI was associated with hyperconstriction of target vessels compared with non-target vessels in patients with a BMS but not with a 2nd-generation DES **(Fig. 4A)**. The proportions of target vessels with large late lumen loss were significantly larger in patients with a BMS (37/53 patients with a BMS and 20/59 patients with a 2nd-generation DES; $P<0.001$ by Fisher's exact test), while large late lumen loss was associated with hyperconstriction of target vessels in patients with a BMS but not with a 2nd-generation DES **(Fig. 4B)**. Finally, 18 of 53 patients with a BMS presented with ACS and large late lumen loss. In this subgroup, constrictive responses in target vessels were even prominent compared to non-target vessels, suggesting

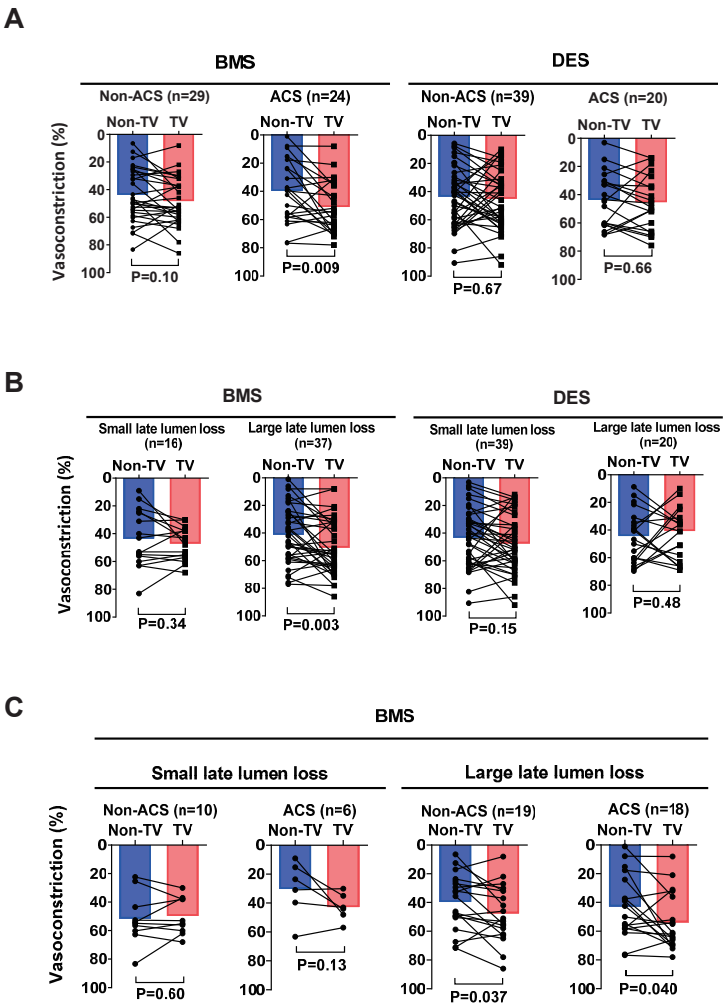

Fig. 4. Vasoconstrictive responses to ACh in patients with a BMS or 2nd-generation DES

A. Comparison of coronary vasoconstrictive responses to ACh between target vessels or non-target vessels among patients with a BMS ($n=53$) or 2nd-generation DES ($n=59$) with or without ACS at the index PCI.

B. Comparison of coronary vasoconstrictive responses to ACh between target vessels or non-target vessels among patients with a BMS ($n=53$) or 2nd-generation DES ($n=59$) with smaller or larger than median late lumen loss.

C. Comparison of coronary vasoconstrictive responses to ACh between target vessels or non-target vessels among patients with a BMS ($n=53$) with or without ACS or large late lumen loss.

ACh, acetylcholine; BMS, bare metal stent; DES, drug-eluting stent; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention

that late lumen loss occurring in ACS-related target vessels treated with a BMS is prone to coronary endothelial dysfunction **(Fig. 4C)**.

Discussion

In this study, we compared vasomotions of target vessels with stents and non-target vessels without stents and found that ACh-induced vasoconstrictive responses of target vessels were not enhanced with a 2nd-generation DES, but significantly enhanced in the coronary arteries with a BMS. We also found that Rho-kinase activity did not differ between patients with BMS and 2nd-generation DES. It has been reported that coronary endothelial dysfunction was observed in the chronic phase following stent implantation with a 1st-generation DES[20] but not with a 2nd-generation DES compared with a BMS[21, 22]. The discrepancy of the results with BMS in the present study and those in the previous studies are discussed from two perspectives.

Comparison of Vasomotion between Stented and Nonstented Arteries

The first perspective is a methodological difference. In above previous studies, coronary responses were compared between different patients. In this study, we investigated the degree of ACh-induced vasoconstriction in target vessel and non-target vessel, assuming the non-target vessel as an internal control in each patient. Using this unique method, we detected endothelial dysfunction in the target vessel with BMS, which might not be detected by conventional methods.

Endothelial Dysfunction in Target Vessel with BMS

Among clinical and angiographic factors, the BMS group included more males, more use of anticoagulant therapy and fewer hypertensive patients **(Table 1)**. Although we did not collect the data about the medical history of atrial fibrillation (AF) or cancer in the CuVIC trial, BMSs might be selected in patients with high bleeding risks to shorten the duration of triple antithrombotic therapy. Previous studies showed that AF is associated with endothelial dysfunction, which may owe to a decreased endotheliun-derived nitric oxide[23]. However, the influence of these systemic factors was controlled in our study by evaluating vasomotion of target vessels comparing with non-target vessels as an internal control, both of which are exposed to systemic factors. Rather than systemic factors mentioned above, ACS at the index PCI and large late lumen loss were associated with hyperconstriction of the target vessel compared with non-target vessel in patietns with BMS **(Table 3)**. It has been reported that vasoconstrictive responses are pronounced in infarct-related arteries compared with noninfarct-related arteries 1-24 months after myocardial infarction, although the mechanism of the difference is unknown[24]. It is speculated that persistent inflammation in the culprit coronary lesions causes delayed endothelialization as well as enhanced neointimal formations[25], although it is not proven in this study. The association between late lumen loss and coronary endothelial dysfunction is explained by a blood flow disturbance, which weakens fluid shear stress that elicits several vasculoprotective responses in endothelial cells including the formation of nitric oxide[26-28]. Indeed, the reduction in shear stress at the vessel wall distal to the arteriosclerotic lesions was associated with lesion restenosis and vascular endothelial dysfunction[29]. The use of 2nd-generation DESs may preserve endothelial function partly through a smaller late lumen loss and therefore preserve physiological shear stress.

Rho-Kinase in DES-Associated Endothelial Dysfunction

Enhanced Rho-kinase activity is reported to play a crucial role in the pathogenesis of coronary hyperconstrictive responses induced by 1st-generation drug-eluting stents (DESs) in pigs[30] and humans[31]. Nishimiya *et al.*[32] reported that Rho-kinase activity was markedly enhanced at the stent edges of the 1st-generation DES and was significantly suppressed at 2nd-generation DES edges in pigs. Although it is possible to evaluate Rho-kinase activity by the inhibitory effects of intracoronary administration of fasudil on acetylcholine-induced coronary vasoconstriction, we avoided off-label use of fasudil in the CuVIC trial and therefore evaluated Rho-kinase activity in circulating mononuclear cells from the coronary sinus, which is a useful biomarker for coronary artery vasospasm[18]. Our study demonstrated that the Rho-kinase activity in circulating leucocytes did not differ between the BMS and the 2nd-generation DES groups, suggesting that the impact of 2nd-generation DES on Rho-kinase activity is not significant as it is reported in 1st-generation DES[30, 31]. Our findngs are in line with the report by Kim *et al.*[33], which showed preserved coronary endothelial function with 2nd-generation DES compared with 1st-generation DES. Drug elution was completed within 120 days (everolimus-eluting stent), 180 days (zotarolimus-eluting stent) or 3-4 months (biodegradable polymer biolimus-eluting stent) according to the manufacturers, which also supports the lack of a difference in Rho-kinase activation between BMSs and 2nd-generation DESs in this study.

Currently, 1st-generation DESs are not used in clinical practice, and the use of BMSs is also limited. Hamilos *et al.*[34] showed that endothelial function was maintained with a BES compared to a sirolimus-eluting stent, indicating that the use of bioabsorbable polymers contributed to appropriate healing of the endothelium. Because coronary endothelial dysfunction is associated with future coronary events, it is important to note that stent-associated coronary endothelial dysfunction is expected to further decrease in the future.

This study has several limitations that we should note. First, this is a retrospective study, even though the stent type was stratified at randomization of the CuVIC trial that assessed the effect of lipid-lowering therapy on coronary endothelial dysfunction. However, we consider that this might not affect our findings since we used QCA with rigorous adjudication by an independent core laboratory that was blinded to the allocated treatment and type of stent. Second, this study is limited by the small

number of study patients, because this study was performed as a subgroup analysis of CuVIC trial without a pre-designed number of cases. Third, we did not evaluate baseline coronary endothelial function. It is unclear whether patients having abnormal endothelial function before stent implantation were present. Fourth, in the CuVIC trial, the intracoronary ACh test was avoided in cases requiring target vessel revascularization due to target vessel failures because of a safety concern. Therefore, the exclusion of patients with severe atherosclerosis burden may become a limitation. Fifth, the effects of ACh on coronary endothelial function are known to be dependent on ethnicity, and Asian individuals show a higher degree of coronary vasoconstriction in response to ACh infusion than Caucasian patients[35].

In conclusion, by evaluating vasomotion of target vessels comparing with non-target vessels, second-generation DESs were not associated with coronary endothelial dysfunction in target vessels compared to nonstented non-target vessels, nor activation of Rho-kinase in the coronary sinus blood 6-8 months after stenting.

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Conflict of Interest

H.T. reports personal fees from Bayer Yakuhin, Pfizer Japan, Otsuka Pharmaceutical, Daiichi Sankyo, MSD, Nippon Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Bristol-Myers Squibb, Novartis Pharma as well as grants from Mitsubishi Tanabe Pharma, Japan Tobacco, Nippon Boehringer Ingelheim, Omron Healthcare, Daiichi Sankyo, Actelion Pharmaceuticals, IQVIA services Japan, Teijin Pharma. T.M. reports grants from Abbott, Amgen, AstraZeneca, Bayer Yakuhin, Kowa, MSD.

Appendix

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Supplementary Table 1. Baseline Clinical Characteristics in Patients with TVFs

	Total (n = 36)	BMS (n = 19)	2nd-Gen DES (n = 17)	p-value
Demographics				
Age (years)	67 ± 12	63 ± 13	70 ± 9	0.061
Male, n (%)	27 (75)	17 (89)	10 (59)	0.055
Body mass index (kg/m^2)	25 ± 4	25 ± 4	24 ± 4	0.42
Heart rate (bpm)	68 ± 11	65 ± 10	72 ± 11	0.038
Systolic blood pressure (mmHg)	125 ± 12	122 ± 14	128 ± 9	0.14
Left ventricular ejection fraction (%)	66 ± 11	63 ± 12	68 ± 9	0.18
Risk factors, n (%)				
Hypertension	31 (86)	15 (79)	16 (94)	0.34
Diabetes mellitus	18 (50)	9 (47)	9 (53)	1.0
Dyslipidemia	32 (89)	16 (84)	16 (94)	0.61
Smoking	12 (33)	9 (47)	3 (18)	0.08
Family history	2 (6)	2 (11)	0 (0)	0.49
Medical treatment, n (%)				
Aspirin	36 (100)	19 (100)	17 (100)	-
$P2Y_{12}$ inhibitor	36 (100)	19 (100)	17 (100)	-
Other antiplatelet	2 (6)	1 (5)	1 (6)	1.0
Anticoagulant	1 (3)	1 (5)	0 (0)	1.0
ARB	19 (53)	8 (42)	11 (65)	0.2
ACE Inhibitor	12 (33)	8 (42)	4 (24)	0.3
β-Blocker	20 (56)	12 (63)	8 (47)	0.5
CCB	18 (50)	7 (37)	11 (65)	0.18
Nitrate	7 (19)	3 (16)	4 (24)	0.68
Statin	36 (100)	19 (100)	17 (100)	-
Ezetimibe	14 (39)	7 (37)	7 (41)	1.0
Antidiabetic agents	13 (36)	9 (47)	4 (24)	0.18
Insulin	5 (14)	0 (0)	5 (29)	0.016
Laboratory tests				
Total cholesterol (mg/dL)	171 ± 45	163 ± 44	181 ± 46	0.26
HDL cholesterol (mg/dL)	44 ± 13	40 ± 13	48 ± 12	0.055
LDL cholesterol (mg/dL)	101 ± 38	94 ± 41	108 ± 35	0.31
Triglyceride (mg/dL)	133 ± 71	141 ± 82	125 ± 56	0.5
Creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.3	0.36
HbA1c (%)	6.4 ± 1.1	6.3 ± 1.1	6.5 ± 1.0	0.43

Variables are n (%) or mean ± S.D.
Abbreviations: BMS: bare metal stent, DES: drug-eluting stent, ARB: angiotensin II receptor blocker, ACE: angiotensin-converting enzyme, CCB: calcium channel blocker, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HbA1c: hemoglobin A1c.

Supplementary Table 2. Angiographical findings at the index PCI and follow-up CAG in Patients with TVFs

	Total (n = 36)	BMS (n = 19)	2nd-Gen DES (n = 17)	p-value
Index PCI				
Acute coronary syndrome, n (%)	13 (36)	9 (47)	4 (24)	0.18
Stent diameter (mm)	3.0 ± 0.4	3.0 ± 0.5	2.9 ± 0.4	0.38
Stent length (mm)	18 ± 6	17 ± 4	20 ± 7	0.15

Variables are n (%) or mean ± S.D.
Abbreviations: BMS: bare metal stent, DES: drug-eluting stent, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, LCx: left circumflex artery, CAG: coronary angiography

Supplementary Table 3. Comparison of Baseline Clinical Characteristics in Patients with or without TVFs

	Total (n = 148)	TVF + (n = 36)	TVF - (n = 112)	p-value
Demographics				
Age (years)	66 ± 10	67 ± 12	66 ± 10	0.63
Male, n (%)	113 (76)	27 (75)	86 (77)	0.82
Body mass index (kg/m^2)	25 ± 4	25 ± 4	25 ± 4	0.84
Heart rate (bpm)	69 ± 11	68 ± 11	70 ± 11	0.5
Systolic blood pressure (mmHg)	123 ± 16	125 ± 12	122 ± 17	0.33
Left ventricular ejection fraction (%)	64 ± 11	66 ± 11	63 ± 11	0.34
Risk factors, n (%)				
Hypertension	100 (68)	31 (86)	69 (62)	0.007
Diabetes mellitus	71 (48)	18 (50)	53 (47)	0.85
Dyslipidemia	135 (91)	32 (89)	103 (92)	0.52
Smoking	50 (34)	12 (33)	38 (35)	1.0
Family history	25 (17)	2 (6)	23 (21)	0.041
Laboratory tests				
Total cholesterol (mg/dL)	173 ± 41	171 ± 45	173 ± 40	0.79
HDL cholesterol (mg/dL)	46 ± 13	44 ± 13	46 ± 13	0.32
LDL cholesterol (mg/dL)	100 ± 35	101 ± 38	99 ± 35	0.82
Triglyceride (mg/dL)	140 ± 74	133 ± 71	142 ± 75	0.53
Creatinine (mg/dL)	0.8 ± 0.3	0.9 ± 0.2	0.8 ± 0.3	0.77
HbA1c (%)	6.3 ± 1.2	6.4 ± 1.1	6.3 ± 1.2	0.58

Variables are n (%) or mean ± S.D.
Abbreviations: BMS: bare metal stent, DES: drug-eluting stent, ARB: angiotensin Ⅱ receptor blocker, ACE: angiotensin-converting enzyme, CCB: calcium channel blocker, HDL: high-density lipoprotein, LDL: low-density lipoprotein, HbA1c: hemoglobin A1c.

Supplementary Table 4. Comparison of Angiographical findings at the index PCI and follow-up CAG in Patients with or without TVFs

	Total (n = 148)	TVF + (n = 36)	TVF - (n = 112)	p-value
Index PCI				
Acute coronary syndrome, n (%)	57 (39)	13 (36)	44 (39)	0.84
Stent Type				
BMS	72 (49)	19 (53)	53 (47)	0.7
2nd-Gen DES	76 (51)	17 (47)	59 (53)	0.7
Stent diameter (mm)	3.1 ± 0.5	3.0 ± 0.4	3.2 ± 0.5	0.048
Stent length (mm)	20 ± 7	18 ± 6	20 ± 7	0.15

Variables are n (%) or mean ± S.D.
Abbreviations: BMS: bare metal stent, DES: drug-eluting stent, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, LCx: left circumflex artery, CAG: coronary angiography