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Second-generation everolimus-eluting stents demonstrate better vascular function, less thrombus formation, and less yellow intima than first-generation drug-eluting stents

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KEYWORDS

- angioscopy
- drug-eluting stent
- endothelial function

Abstract

Aims: We compared endothelial function and intra-stent condition after second-generation everolimus-eluting stent (EES) versus first-generation drug-eluting stent (DES) implantation.

Methods and results: We enrolled 117 patients with stable angina who were treated with EES (n=44), sirolimus-eluting stents (SES) (n=43), and paclitaxel-eluting stents (PES) (n=30). At nine-month follow-up, endothelial function was evaluated by intracoronary acetylcholine (Ach) infusion. Vascular responses to Ach were quantitatively measured. With angioscopy, cases were assessed for: 1) the degree of neointimal coverage (grade 0: no coverage, to 3: full coverage); 2) presence of in-stent thrombus; and 3) existence of yellow intima. Vasomotion to Ach distal to the EES was better preserved than to the SES and PES (vs. SES; $p<0.01$ and vs. PES; $p<0.01$), while vasomotions to Ach proximal to the stent were comparable among the three groups ($p=0.12$). From the angioscopic study, the incidences of in-stent thrombus and yellow intima in the EES group were significantly lower than in the SES and PES groups (thrombus - EES: 6.8%, SES: 27.9%, PES: 60.0%; $p<0.01$, yellow intima - EES: 11.4%, SES: 51.2%, PES: 36.7%, $p<0.01$), whereas the neointimal coverage was similar among the three groups ($p=0.44$).

Conclusions: EES demonstrated better endothelial function, less thrombus formation, and less yellow intima than first-generation DES at nine-month follow-up.

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Abbreviations

Ach	acetylcholine
BMS	bare metal stents
DES	drug-eluting stents
EES	everolimus-eluting stents
NTG	nitroglycerine
PCI	percutaneous coronary intervention
PES	paclitaxel-eluting stents
QCA	quantitative coronary angiography
SES	sirolimus-eluting stents
ST	stent thrombosis

Introduction

Drug-eluting stents (DES) have significantly reduced in-stent restenosis and target lesion revascularisation after percutaneous coronary intervention (PCI) as compared with bare metal stents (BMS)[1,2]. In spite of these benefits, concern over increased stent thrombosis (ST) still exists[3]. Although the incidences of ST are low, ST is an immediate life-threatening complication and may occur consistently up to at least five years after implantation of first-generation DES, sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES)[4,5]. Several pathophysiological factors could be associated with ST, such as delayed re-endothelialisation, incomplete stent strut coverage, prolonged inflammation, hypersensitivity reactions, late acquired malapposition, strut fractures, and neoatherosclerosis[6-10]. In particular, delayed re-endothelialisation and incomplete stent strut coverage have been considered as significant factors with regard to ST in human autopsy studies[7,8]. The use of durable polymer coating, the thickness of the stent struts, and the dose of the antiproliferative drug and its release kinetics in first-generation DES have been implicated as important contributory factors in these issues[11-13].

Meanwhile, second-generation DES, including everolimus-eluting stents (EES), have been developed with different drugs, more biocompatible polymers, improved drug release kinetics and thinner stent struts. Indeed, EES showed better outcomes including a lower risk of ST compared with first-generation DES in real-world patients[14-16]. This favourable clinical performance might be associated with better vascular response to EES. However, there have been few investigations on endothelial function and arterial healing in EES[17,18].

Coronary angioscopy is a unique imaging modality that allows inspection macroscopic pathology in living patients and direct visualisation of luminal structure such as atherosclerotic plaque, thrombus, stent struts, and proliferating neointima.

The aim of this study was to evaluate coronary endothelial function and intra-stent condition using angioscopy in patients at nine months after EES implantation, and to compare these data with first-generation DES results.

Methods

STUDY PROTOCOL

This single-centre, non-randomised study involves 48 patients implanted with EES (XIENCE™; Abbott Vascular, Santa Clara, CA, USA), included prospectively from January 2011 to January 2013, together with 46 patients implanted with SES (CYPHER™; Cordis Corporation, Miami Lakes, FL, USA) and 36 patients implanted with PES (TAXUS™; Boston Scientific Corporation, Natick, MA, USA), included prospectively from January 2009 to December 2011. Some of these study data regarding patients with SES (n=40) and PES (n=26) were included in our previous report[19]. Eligible subjects were diagnosed with stable effort angina and treated with a single DES for a *de novo* single lesion. All stents were implanted using standard PCI techniques. Follow-up coronary angiography, coronary endothelial function evaluation and coronary angioscopy were performed at nine months after PCI. Exclusion criteria for this study were: acute and old myocardial infarction, clinical or angiographic history of coronary vasospasm, previous coronary bypass graft surgery, left main coronary artery lesion, bifurcation lesion requiring two stents, chronic total occlusions, in-stent restenosis lesion, angiographic in-stent restenosis by follow-up angiography, symptomatic congestive heart failure, severe left ventricular dysfunction (ejection fraction <30%) and severe valvular heart disease. This study was approved by the ethics committee of our institution and all patients provided written informed consent.

MEDICATION REGIMEN

All patients received aspirin (100 mg/day) and clopidogrel (75 mg/day) during the follow-up period. Statins and renin-angiotensin system inhibitors including angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) were administered daily to all patients wherever possible, because these drugs may have salutary effects on coronary endothelial function[20-22].

EVALUATION OF CORONARY ENDOTHELIAL FUNCTION

Coronary endothelial function was estimated by measuring coronary vasomotion in response to acetylcholine (Ach) at nine-month follow-up. All vasoactive medications, including calcium channel blockers, long-acting nitrates, ACEI, ARB and β-blockers, were discontinued at least 24 hours before the test. After baseline angiography, endothelium-dependent vasomotor response was evaluated by using an intracoronary infusion of Ach in incremental doses at 10^{-7} and 10^{-6} mol/L for two minutes. At least three minutes were allowed between each infusion. If clinically needed, a temporary pacemaker was inserted through the femoral vein. Subsequently, endothelium-independent vasomotor response was tested after an intracoronary bolus infusion of nitroglycerine (NTG, 200 μg). Angiography was repeated every 30 seconds for two minutes after each drug infusion. The maximal vasomotor responses to Ach and NTG were determined by quantitative coronary angiography (QCA) with a CAAS II system (Pie Medical Imaging BV, Maastricht, The Netherlands). QCA measurements were performed by an independent blinded reviewer. Two segments, 5~25 mm proximal and distal to the stent, were analysed. Additionally, as a reference, an angiographically normal segment in another vessel was evaluated. If the stent was in the right coronary artery, an angiographically normal segment as far away as possible from the stent was analysed as the

reference. The same segments were identified by anatomical landmarks and assessed at each measurement. Changes in vessel diameter in response to Ach and NTG infusion were calculated as the percentage of changes versus the baseline coronary diameter.

ANGIOSCOPIC PROCEDURES AND EVALUATION

After assessment of endothelial function, coronary angioscopy was performed using a balloon occlusion type of angioscopy device (Vecmova NEO™; FiberTech Corporation, Tokyo, Japan). Details regarding the procedure and specifications for these devices have been described elsewhere[23]. Briefly, the angioscopic fibre was placed distal to the stent and was pulled back manually, from distal to proximal segment of the stent, under careful angioscopic and angiographic guidance. When the field of view was flushed clear of blood with Lactated Ringer's solution, inflation of the occlusion balloon was constantly maintained. Each angioscopic image acquisition took about 20 seconds, and all sequences were recorded for subsequent off-line analysis. Angioscopic images were evaluated with a focus on the following: 1) the dominant degree of neointimal coverage over the stent, 2) presence of thrombus inside the stent, and 3) existence of yellow intima over and underneath the stent **(Figure 1)**. The degree of neointimal coverage over the stent was classified into four grades as previously described[19,24-26]: grade 0, fully visible stent struts similar to immediately after stent implantation; grade 1, stent struts with very thin neointimal coverage, but protruded into the lumen and transparently visible; grade 2, stent struts embedded by neointima but seen translucently; and grade 3, stent struts fully embedded and not visible by angioscopy. If various grades were seen in the stent, the dominant pattern in the entire stent was used as the grade of the stent.

Statistical analysis

Statistical analysis was performed using the SPSS Version 22.0 (IBM Corp., Armonk, NY, USA). All continuous data are given as mean±standard deviation or median and interquartile range, according to their normal or non-normal distribution. One-way analysis of variance (ANOVA) with a Scheffe test for multiple comparisons was used in continuous variables. If data were skewed, Kruskal-Wallis was applied and followed by a Mann-Whitney test with Bonferroni correction for multiple comparisons. Categorical variables are presented as number (n) or percentage (%). The chi-square test with Bonferroni adjustment was used in categorical variables. The group differences on % changes in vessel diameter were tested by two-way ANOVA for repeated measurements with a Scheffe test for multiple comparisons. To identify factors that were independently associated with endothelial dysfunction, linear regression analyses were used. Including only variables with $p<0.05$ on simple linear regression test, forward stepwise multivariate regression analysis was performed. A two-tailed p-value less than 0.05 was considered statistically significant.

Results

Follow-up angiography was not performed in seven patients (three patients with EES, two patients with SES, and two patients with PES). Additionally, the segment proximal to the stent could not be

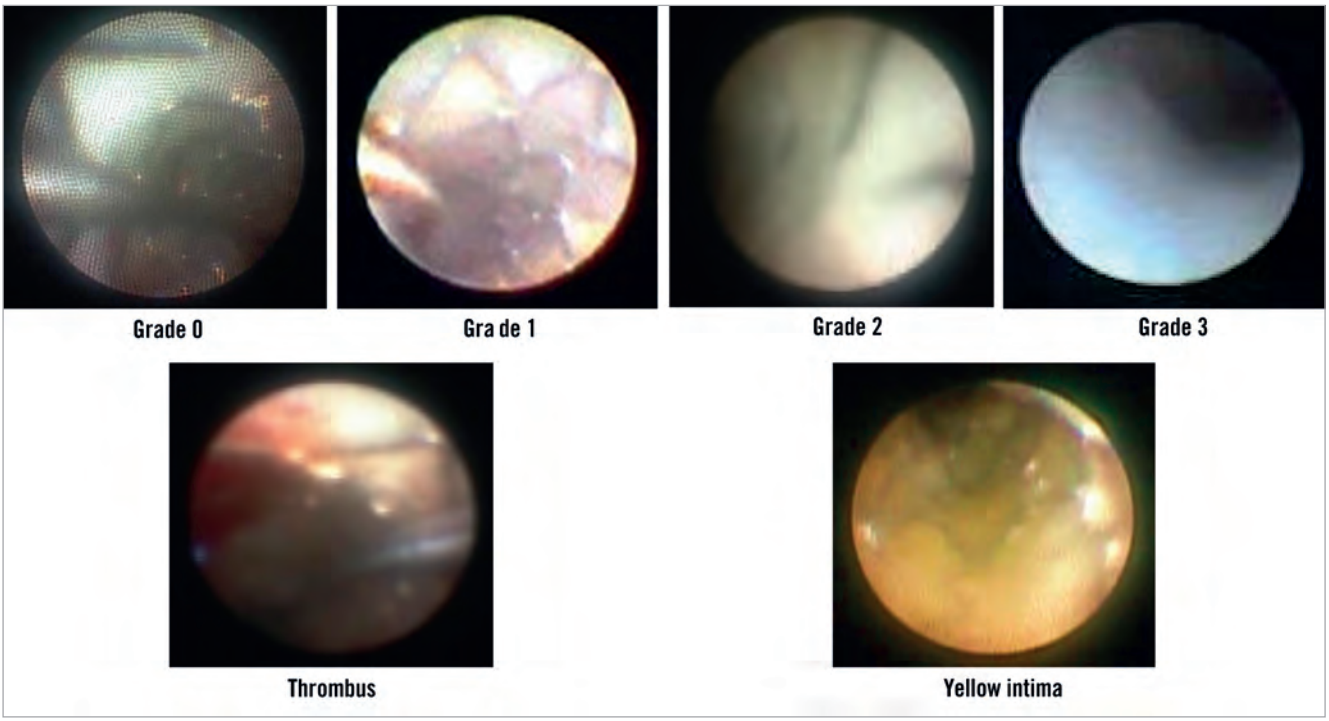

Figure 1. *Angioscopic images of neointimal coverage grade, thrombus and yellow intima. Grade 0: fully visible stent struts similar to immediately after stent implantation. Grade 1: stent struts with very thin neointima, but protruded into the lumen and transparently visible. Grade 2: stent struts embedded by neointima but seen translucently. Grade 3: stent struts fully embedded and not visible. Thrombus: red thrombus formation inside the stent; yellow intima: yellow intima over and underneath the stent.*

evaluated in four patients (one patient with EES and three patients with PES) due to ostial stent location, and clear angioscopic images could not be obtained in two patients (one patient with SES and one patient with PES).

As a result, a total of 117 patients (44 patients with EES, 43 patients with SES, and 30 patients with PES) were included in the analysis.

Baseline patient, lesion, and procedural characteristics are shown in **Table 1**. There were significant differences in the stent diameter and the stent deployment pressure among the three groups. Follow-up patient data are listed in **Table 2**. No significant differences were found in follow-up patient characteristics among the groups. At follow-up, late loss in the PES group was significantly greater than in the SES and EES groups **(Table 3)**. No adverse cardiac events occurred during the follow-up period and no patients showed in-stent restenosis on follow-up angiography in all three groups.

Table 1. Baseline patient, lesion, and procedural characteristics.

	EES (n=44)	SES (n=43)	PES (n=30)	*p*-value
Age	70.5±9.3	69.8±9.1	67.5±8.8	0.36
Men	32 (72.7%)	33 (76.7%)	21 (70.0%)	0.81
Hypertension	37 (84.1%)	32 (74.4%)	22 (73.3%)	0.44
Dyslipidaemia	28 (63.6%)	25 (58.1%)	13 (43.3%)	0.22
Diabetes mellitus	22 (50.0%)	26 (60.5%)	22 (73.3%)	0.13
Smoking	16 (36.4%)	19 (44.2%)	10 (33.3%)	0.60
LVEF (%)	64.3±8.9	63.7±11.8	66.0±7.2	0.59
Medications				
Statin	27 (61.4%)	24 (55.8%)	17 (56.7%)	0.86
ACEI or ARB	26 (59.1%)	22 (51.2%)	18 (60.0%)	0.68
Calcium channel blocker	21 (47.7%)	18 (41.9%)	16 (53.3%)	0.62
β-blocker	23 (52.3%)	16 (37.2%)	10 (33.3%)	0.20
Pre diameter stenosis (%)	81.9±12.3	77.7±12.6	77.4±11.7	0.18
Type B2 or C	29 (65.9%)	24 (55.8%)	16 (53.3%)	0.49
Stent diameter (mm)	3.0±0.4	2.9±0.4	3.2±0.3*	<0.01
Stent length (mm)	25.2±6.7	24.5±6.4	24.6±6.1	0.86
Stent deployment pressure (atm)	11.1±2.8	13.3±3.6¶	11.6±2.7	<0.01
Coronary artery lesion				0.41
LAD	22 (50.0%)	21 (48.8%)	19 (63.3%)	
LCX	14 (31.8%)	14 (32.6%)	4 (13.3%)	
RCA	8 (18.2%)	8 (18.6%)	7 (23.3%)	

Values are mean±standard deviation or number (%). *vs. SES, $p<0.01$; vs. EES, $p<0.05$. ¶vs EES, $p<0.01$. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; LAD: left anterior descending artery; LCX: left circumflex artery; LVEF: left ventricular ejection fraction; RCA: right coronary artery

Table 2. Patient characteristics at follow-up.

	EES (n=44)	SES (n= 43)	PES (n=30)	*p*-value
Follow-up period (months)	8.5±3.1	9.3±2.1	9.9±2.9	0.09
Medications				
Statin	39 (88.6%)	42 (97.7%)	30 (100%)	0.05
ACEI or ARB	42 (95.5%)	42 (97.7%)	30 (100%)	0.48
Calcium channel blocker	21 (47.7%)	18 (41.9%)	15 (50.0%)	0.76
β-blocker	23 (52.3%)	23 (53.5%)	11 (36.7%)	0.31
Aspirin + clopidogrel	44 (100%)	43 (100%)	30 (100%)	1.00

Values are mean±standard deviation or number (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 3. Angiographic and angioscopic findings at follow-up.

	EES (n=44)	SES (n=43)	PES (n=30)	*p*-value
In-stent late loss (mm)	0.05 (0.00-0.22)	0.01 (0.00-0.10)	0.46±0.35*	<0.01
Grade of strut coverage	1.45±0.82	1.37±1.00	1.67±1.12	0.44
In-stent thrombus	3 (6.8%)¶	12 (27.9%)	18 (60.0%)	<0.01
Yellow intima	5 (11.4%)‡	22 (51.2%)	11 (36.7%)	<0.01

Values are mean±standard deviation, median (interquartile range), or number (%). *vs. SES; $p<0.01$, vs. EES; $p<0.01$. ¶vs. SES; $p<0.05$, vs. PES; $p<0.01$. ‡vs. SES; $p<0.05$, vs. PES; $p<0.05$.

CORONARY ENDOTHELIAL FUNCTION

At the reference segments and segments proximal to the stent, coronary vasomotor responses to Ach and NTG were comparable among the three groups (p=0.46 and p=0.12, respectively) **(Figure 2)**. In contrast, vascular responses to Ach distal to the stent in the EES group were better preserved than in the SES and PES

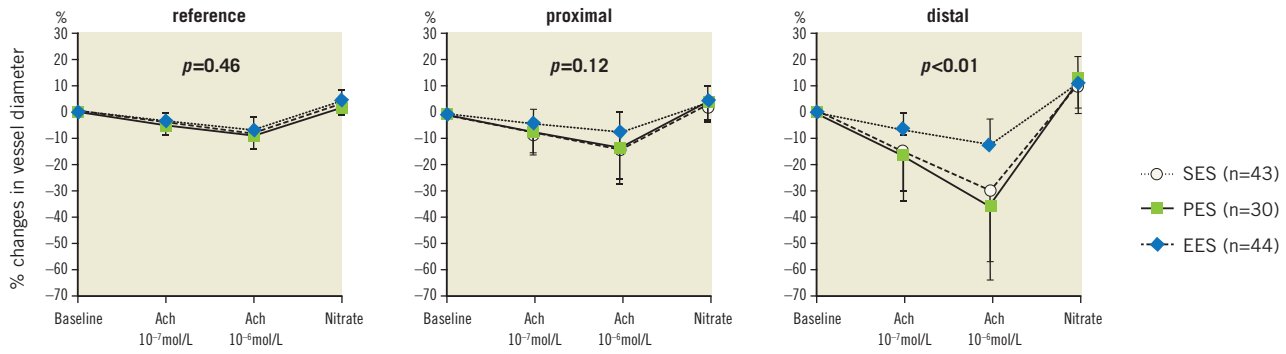

Figure 2. *Changes in vessel diameter in response to Ach and NTG infusion expressed as percentage of changes versus the baseline diameter. p-values indicate differences among the three groups. Ach: acetylcholine; NTG: nitroglycerine*

groups (p<0.01 in ANOVA; EES vs. SES, p<0.01; EES vs. PES, p<0.01; SES vs. PES, p=0.84) **(Figure 2)**.

ANGIOSCOPIC FINDINGS

Angioscopic data at follow-up are listed in **Table 3**. Incidences of in-stent thrombus and yellow intima in the EES were significantly lower than in the SES and PES groups (p<0.01 and p<0.01, respectively), while the average of dominant neointimal coverage grading was comparable among the three groups (p=0.44).

INDEPENDENT FACTORS OF ENDOTHELIAL DYSFUNCTION DISTAL TO THE STENT AFTER DES IMPLANTATION

A linear regression analysis was performed to determine the factors of vasomotor response to maximum dose of Ach (10^{-6} mol/L) distal to the stent. No patient or lesion variables were associated with the vasomotive reactions to Ach distal to the stent. The presence of yellow intima and the grade of neointimal coverage were significantly associated with vasoconstriction to Ach distal to the stent in a simple linear regression, but not in a stepwise multivariate regression. In a stepwise multivariate regression analysis, the presence of in-stent thrombus and the generation of DES (first/second) were determined to be the independent factors of endothelial dysfunction distal to the stent after DES implantation (p<0.001 and p<0.001, respectively) **(Table 4)**.

Table 4. Independent factors of endothelial dysfunction* after DES implantation.

	Stepwise multivariate regression		
	β coefficient	*p*-value	Adjusted R^2
Presence of in-stent thrombus	0.40	<0.01	0.31
First-generation/second-generation	0.29	<0.01	

*Vascular motion in response to acetylcholine (10^{-6} mol/L) at segment distal to DES.
DES: drug-eluting stent

Discussion

The main findings of the present study were the following. 1) Coronary vasomotions to Ach distal to the EES were better preserved than those of first-generation DES. 2) Incidences of in-stent thrombus formation and yellow intima with the EES were significantly lower than with the first-generation DES. 3) The presence of in-stent thrombus and the generation of DES were the independent factors of endothelial dysfunction distal to the DES.

Coronary endothelial dysfunction has been suggested to be an independent predictor of atherosclerotic disease progression and cardiovascular event rates[27]. Likewise, incomplete neointimal coverage and yellow intima could be related with an increased potential risk of future thrombotic events in DES[7,8,28-31]. In addition, the presence of in-stent thrombus would indicate lack of re-endothelialisation and/or endothelial dysfunction at the stented site.

There are numerous clinical data showing delayed arterial healing after first-generation DES implantation[19,24-26]. Components including durable polymers and thick stent struts in first-generation DES contributed to the delayed healing[11-13]. Moreover, several clinical studies of first-generation DES have revealed endothelial dysfunction at adjacent segments, especially in distal segments[19,32-34]. Although there is no definitive explanation for abnormal endothelial function adjacent to DES, there are several potential mechanisms to be considered. First, re-endothelialisation has been reported to be seriously delayed after first-generation DES implantation[7,8]. Accordingly, reduced nitric oxide production attributable to delayed re-endothelialisation at the stented site could be associated with endothelial dysfunction adjacent to the DES. Second, Sahler et al showed that antiproliferative drugs may have locally diffused through the vasa vasorum to the non-stented distal segments, leading to impaired endothelial function distal to the DES[35]. Third, Pendyala et al reported that polymer incompatibility and potentiation of superoxide activity may be a culprit of endothelial dysfunction with PES[36]. Fourth, as we have previously reported in the canine model of acute coronary syndromes, vasoactive substances released from thrombi, which are shed into the distal site and would impair distal endothelial function, may also play a critical role[37,38]. Furthermore, we have shown that endothelial dysfunction distal to first-generation DES was strongly associated with the existence of in-stent thrombus in the clinical setting[19]. Thus, thrombus at the stent site might aggravate endothelial function adjacent to the DES.

ARTERIAL HEALING AND ENDOTHELIAL FUNCTION AFTER EES IMPLANTATION

In the current study, the use of EES was associated with better-preserved endothelial function, less in-stent thrombus formation, and less yellow intima compared with first-generation DES, whereas EES did not show superiority in the grade of neointimal coverage.

EES consist of a thin strut platform coated with a durable fluoropolymer. Thin stent struts are associated with less arterial injury, less flow disturbance, more rapid endothelial cell coverage, and less thrombogenicity compared to thick stent struts[39-41]. Additionally, fluoropolymers of EES have also demonstrated thromboresistant properties with more rapid endothelialisation tendencies in several *ex vivo* and *in vivo* experiments[40,41]. Thus, better re-endothelialisation and less thrombus formation with EES may lead to better endothelial function than first-generation DES.

Yellow intima is considered as unstable plaque and could be related to future clinical events[28-31]. Previous angioscopic studies have revealed that yellow intima was more often observed after first-generation DES, especially SES implantation, compared with BMS[25,26]. Moreover, it has been reported that the yellow colour of plaque changes to a stable white colour during the six months after BMS implantation[42]. By contrast, in first-generation DES, incomplete neointimal coverage and chronic inflammation may be attributed to prolonged yellow intima exposure. EES treatment is associated with fewer inflammatory responses compared with first-generation DES[43]. Therefore, more stable healing processes might lead to a lower incidence of yellow intima in EES than in

first-generation DES, although neointima thickness in EES was comparable to first-generation DES.

Study limitations

Several important limitations of this study should be noted. First, this study was a non-randomised, non-consecutive enrolment and single-centre study with a relatively small number of patients. Additionally, patients were included in different time periods. However, stent selection bias was minimal and has probably not influenced the result, because stent selection was based only on stent availability over time. Indeed, there were no significant differences in baseline patient and lesion characteristics among the three groups. Second, only patients who were diagnosed with stable angina and treated with a single DES for a *de novo* single lesion were evaluated in this study. Therefore, our results may have a risk of patient selection bias and cannot be generalised to all patients in the real world. Third, because our study ended at nine months after DES implantation, our results refer to this specific point in time. Fourth, no baseline angioscopic data were available, although the frequency of yellow intima and thrombus at follow-up should be affected by conditions immediately after stent implantation. Presumably, however, the index frequency of yellow intima and thrombus was similar among the three groups as judged from the similarity of the baseline patient, lesion, and procedural characteristics. Fifth, the initial coronary endothelial function test was not performed. However, the initial endothelial function test could not be applied, because all patients had significant coronary lesions and the presence of significant stenosis would affect vasomotor response. To compensate for this limitation, we evaluated a reference segment as an internal, patient-specific control. Finally, the clinical outcome of our results in the long term remains unknown.

Conclusions

In this study, second-generation EES demonstrated better endothelial function, less thrombus formation, and less yellow intima than first-generation DES at nine months after stent implantation.

Impact on daily practice

It is very important to evaluate coronary endothelial function and intra-stent condition in patients treated with DES, because both endothelial dysfunction and delayed arterial healing could be associated with future cardiovascular event rates. The present study is the first report to reveal that second-generation EES produce better endothelial function and arterial healing than first-generation DES. Our results suggest second-generation EES treatment could provide superior clinical outcomes compared to first-generation DES.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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