Assessment of Second- and Third-Generation Drug-Eluting Stents on Chronic Coronary Angioscopy
— Multicenter Study on Intra-Coronary AngioScopy After Stent (MICASA) Prospective Data Analysis —

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Background: The vascular response, in terms of quality and quantity, of the second- and third-generation drug-eluting stents (2G- and 3G-DES, respectively) was assessed prospectively on coronary angiography (CAS).

Methods and Results: The Multicenter study on Intra-Coronary AngioScopy After Stent (MICASA) is a multicenter CAS registry. A total of 107 DES (71 2G- and 36 3G-DES) were prospectively observed on CAS 8.7±2.7 months after percutaneous coronary intervention. Neointimal coverage (NC) grade was evaluated using a 4-point grading scale, from 0 (no coverage) to 3 (complete coverage). Plaque yellow color (YC) was also assessed using a 4-point grading system, from 0 (white) to 3 (bright yellow). Max-NC (2G-DES vs. 3G-DES: 2.14±0.68 vs. 2.44±0.73, P=0.023); min-NC (1.07±0.48 vs. 1.39±0.60, P=0.002), and dominant-NC (1.57±0.69 vs. 2.08±0.84, P=0.002) were significantly higher and the YC grade (1.23±0.82 vs. 0.86±0.76, P=0.031) significantly lower in the 3G-DES group than in the 2G-DES group. There was no significant difference in the presence of thrombus (28.2% vs. 22.2%, P=0.51) between the 2G- and 3G-DES groups.

Conclusions: The higher NC grade and lower YC grade in 3G-DES than in 2G-DES might be associated with better long-term clinical outcome, which remains to be determined in future studies.

Key Words: Coronary angioscopy; Second-generation drug-eluting stent; Third-generation drug-eluting stent

First-generation (1G) drug-eluting stents (DES) dramatically reduced the rate of in-stent restenosis and target lesion revascularization (TLR) compared with bare metal stents (BMS).1,2 These stents, however, were also known to cause late and very late stent thrombosis, neoatherosclerosis3 and peri-stent contrast staining4 due to poor biocompatible polymer or prolonged drug elution. Thus, the 1G-DES was changed to the second-generation DES (2G-DES), and these problems were thought to be solved. Some problems, however, still exist: thin neointimal coverage (NC) of residual yellow plaque and neoatherosclerosis.5 In the third-generation DES (3G-DES), the drugs are delivered over 3 months, and the polymers break down completely in 4 months. Although the neointima of 2G- and 3G-DES stent struts have been examined on optical coherence tomography (OCT), the assessment of vascular response of 2G-DES and 3G-DES,6 in terms of quality and quantity, using coronary angioscopy (CAS), is still unclear.

Methods

Patients
The Multicenter Study on Intra-Coronary Angioscopy after Stent (MICASA) is a prospective multicenter CAS registry conducted in 5 Japanese institutions. The DES of 185 patients were observed using CAS after percutaneous coronary intervention (PCI) between 1 August 2014 and 31 March 2017. From this group, 119 patients were observed after PCI for 4–18 months (mean, 8.7±2.7 months). Five BMS patients, 4 zotarolimus-eluting stent (ZES) patients, 1 patient with drug-coated balloon, 1 patient with covered stent, and 1 patient with missing data were excluded. A total of 71 lesions were treated with 2G-DES: 32 lesions were implanted with durable-polymer everolimus-eluting
185 patients assessed between Aug 1st 2014 - Mar 31st, 2017

119 patients assessed after PCI from 4 to 18 months (8.7 ± 2.7 months)

- 5 bare metal stents, 4 ZES
- 1 drug coated balloon, 1 graftmaster, 1 missing data

71 patients (2G-DES)
8 BES 32 DP-EES 31 R-ZES
※ 1 case: hybrid stent (DP-EES+R-ZES)

36 patients (3G-DES)
26 BP-SES, 10 BP-EES

Figure 1. Flow chart of patient inclusion. 2G-DES, 2nd-generation drug-eluting stent; 3G-DES, 3rd-generation drug-eluting stent; BES, biolimus-eluting stent; BP, bioresorbable polymer; DP, durable polymer; EES, everolimus-eluting stent; MICASA, Multicenter Study of Intra-Coronary Angioscopy After Stent; PCI, percutaneous coronary intervention; R, slow-release; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

Neointimal Coverage grade (NC grade)

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
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Yellow color grade (YC grade)

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Figure 2. Definitions of (Upper) neointimal coverage (NC) grade and (Lower) yellow color (YC) grade.

stents (DP-EES: Xience V®, Abbott Vascular, Santa Clara, CA, USA, n=24; Promus Element™, Boston Scientific, Natick, MA, USA, n=8); 31 lesions were implanted with slow-releasing ZES (R-ZES: Resolute Integrity™, Medtronic, Minneapolis, MN, USA); 8 lesions with biolimus-eluting stents (BES, Nobori®; Terumo, Tokyo, Japan); and 1 lesion with hybrid stents (DP-EES+R-ZES). A total of 36 lesions were treated with 3G-DES: 26 lesions were implanted with bioresorbable polymer sirolimus-eluting stents (BP-SES; Ultimaster® Terumo), and 10 lesions were implanted with BP-EES (Synergy™, Boston Scientific). We did not enroll patients with in-stent restenosis (Figure 1). Informed consent was given by each patient and the study protocol was reviewed and approved by the ethics committee of each hospital.

CAS
Catheterization was performed with a radial, brachial or femoral approach using ≥6-F guiding catheters. CAS was performed with the FT-203F (FiberTech Co. Ltd., Tokyo,
Results

Baseline Characteristics
The clinical characteristics of the 2G- and 3G-DES groups are listed in Table. Dual antiplatelet therapy (DAPT) was discontinued by the time of CAS more frequently in the 3G-DES group. There was no difference between the 2 groups in terms of etiology (acute coronary syndrome [ACS] or stable angina pectoris). The duration from PCI to CAS was shorter in the 3G-DES group than in the 2G-DES group (8.8 ± 2.6 months vs. 10.1 ± 2.9 months, P=0.026). The lesion in the left anterior descending artery was more frequently higher in the 2G-DES group than in the 3G-DES group (P=0.024).

Statistical Analysis
JMP version 12 (SAS Institute, Cary, NC, USA) was used to analyze the results. All continuous variables are given as mean ± SD. Comparisons between the 2G- and 3G-DES groups were analyzed using Student’s t-test for continuous variables and chi-squared test for discrete variables. Wilcoxon’s test was used to analyze the ordinal variables, in particular CAS findings (NC grade, YC grade). Multivariable logistic regression analysis was performed to identify the independent factors for YC grade (YC grades 2 and 3) and the presence of thrombus. P<0.05 was considered to be statistically significant.

CAS
The CAS findings regarding NC grade are shown in Figure 1. Max-NC (2G-DES vs. 3G-DES: 2.14±0.68 vs. 2.44±0.73, P=0.023), min-NC (1.07±0.48 vs. 1.39±0.60, P=0.002), and dominant-NC (1.57±0.69 vs. 2.08±0.84, P=0.002) grades were significantly higher in the 3G-DES group than in the 2G-DES group. There was no significant difference in HI (1.07±0.68 vs. 1.05±0.67, P=0.85). YC grade (1.23±0.82 vs. 0.86±0.76, P=0.031) was significantly lower in the 3G-DES group than in the 2G-DES group. There was no significant difference in incidence of thrombus (28.2% vs. 22.2%, P=0.51) between the 2 groups. On multivariate analysis, hemoglobin A1c (HbA1c; OR, 3.56; 95% CI: 1.42–8.92, P=0.028) and morbidity of diabetes Japan) non-obstructive coronary angioscope system and the VISIBLE (FiberTech Co. Ltd.) optical fiber. Stented lesions were observed angioscopically, while blood was cleared from the field of view using an injection of 3% dextran, as previously reported.7 Angioscopy was recorded using a digital recorder. Each CAS analysis was performed as agreed by 2 independent cardiologists.

Evaluation NC grade was evaluated using a 4-point grading scale, from 0 (no coverage) to 3 (complete coverage). We determined maximum (max-) and minimum (min-) NC, dominant-NC grades, and heterogeneity index (HI: max-NC grade minus min-NC grade). Plaque yellow color (YC) was assessed using a 4-grade system, from 0 (white) to 3 (bright yellow). We recorded the maximum YC grade visible for each patient. The presence of thrombus was also assessed (Figure 2).*

Statistical Analysis
JMP version 12 (SAS Institute, Cary, NC, USA) was used to analyze the results. All continuous variables are given as mean ± SD. Comparisons between the 2G- and 3G-DES groups were analyzed using Student’s t-test for continuous variables and chi-squared test for discrete variables. Wilcoxon’s test was used to analyze the ordinal variables, in particular CAS findings (NC grade, YC grade). Multivariable logistic regression analysis was performed to identify the independent factors for YC grade (YC grades 2 and 3) and the presence of thrombus. P<0.05 was considered to be statistically significant.
Previously, Nakazawa et al reported the existence of a new atherosclerosis caused by inflammation of 1G-DES, known as “neoatherosclerosis”. It was well-known that 1G-DES decreased in-stent restenosis, but late and very late stent thrombosis and the late-catch up phenomenon emerged as new problems. Use of a biocompatible polymer and improvement in the pharmacokinetics of drug elution were expected to resolve these problems, but neoatherosclerosis still occurred, even in 2G-DES. The DESNOTE study showed that the presence of atherosclerosis at follow-up, with or without yellow plaque immediately after PCI, was responsible for the very late stent failure (VLSF). In the DESNOTE study, 360 patients underwent CAS 1 year after DES implantation (1G- and 2G-DES). Patients were classified according to the presence of yellow neo-intima within the stent, and the incidences of VLSF, cardiac death, myocardial infarction related to the target lesion, and TLR, were compared. During the follow-up interval of 4.3±2.4 years, VLSF occurred more frequently in patients with yellow plaque than in those without yellow plaque. The DESNOTE study suggested that early detection of neoatherosclerosis using CAS can predict VLSF. The 3G-DES is able to elute drugs (sirolimus or everolimus) on multivariate analysis. We conducted this study to evaluate the clinical efficacy of 3G-DES at mid-term follow-up using CAS. The 3G-DES group had lower YC grade than the 2G-DES group, which may be due to the lower level of neoatherosclerosis in 3G-DES than in 2G-DES or to the difference in baseline patient background between the 3G- and 2G-DES groups. Previously, Nakazawa et al reported the existence of a new atherosclerosis caused by inflammation of 1G-DES, known as “neoatherosclerosis”. It was well-known that 1G-DES decreased in-stent restenosis, but late and very late stent thrombosis and the late-catch up phenomenon emerged as new problems. Use of a biocompatible polymer and improvement in the pharmacokinetics of drug elution were expected to resolve these problems, but neoatherosclerosis still occurred, even in 2G-DES. The DESNOTE study showed that the presence of atherosclerosis at follow-up, with or without yellow plaque immediately after PCI, was responsible for the very late stent failure (VLSF). In the DESNOTE study, 360 patients underwent CAS 1 year after DES implantation (1G- and 2G-DES). Patients were classified according to the presence of yellow neo-intima within the stent, and the incidences of VLSF, cardiac death, myocardial infarction related to the target lesion, and TLR, were compared. During the follow-up interval of 4.3±2.4 years, VLSF occurred more frequently in patients with yellow plaque than in those without yellow plaque. The DESNOTE study suggested that early detection of neoatherosclerosis using CAS can predict VLSF. The 3G-DES is able to elute drugs (sirolimus or everolimus)
after 3 months and resorb polymer after 4 months. The lower YC grade in the 3G-DES group than in the 2G-DES group may explain the lower rate of neoatherosclerosis.

Dai et al compared BMS to 1G- and 2G-DES using CAS in a MICASA retrospective study. Max-NC and min-NC grades were lower in the 1G- and 2G-DES groups than in the BMS group. Moreover, the max-NC grade for the 2G-DES was similar to that with the 1G-DES, but the min-NC grade was higher in the 2G-DES group; the HI, YC grade, and incidence of thrombus were all lower in the 2G-DES than in the 1G-DES group, which in turn was similar to the BMS group. The Dai et al study used both prospective and retrospective data, but in the present study we used only prospective data. From that prospective study, 3G-DES that changes BMS in 4 months after PCI may be efficient to prevent stent failure.

The CENTURY II trial demonstrated the non-inferiority of BP-SES to permanent polymer-EES (PP-EES) in terms of the target lesion failure (TLF) at mid-term follow-up (approximately 9 months). Kuramitsu et al reported a substudy of the CENTURY II trial, on “the vascular response of BP-SES vs. PP-EES using optical coherence tomography”. There were no significant differences between BP-SES and PP-EES in terms of strut coverage (BP-SES vs. PP-EES: 98.98% vs. 97.74%, P=0.35) and mean neointimal thickness (BP-SES vs. PP-EES: 110±10 μm vs. 93±9 μm, P=0.22). The vascular response of BP-SES and DP-EES was similar. In the CENTURY II substudy, BP-SES was expected to have a good clinical outcome similar to PP-EES. That study, however, did not investigate whether thromb, neointima and mural thrombus could be differentiated on OCT, therefore thrombi may appear as neointima on OCT.

In this prospective study, DM and HbA1c were associated with YC grade and dyslipidemia was correlated with thrombus. The correlation between DM and YC grade has been previously reported. This may be due to the level of high-sensitivity C-reactive protein, which was significantly higher in patients with DM than in those without. Vascular inflammation may be associated with YC grade. In contrast, dyslipidemia was associated with thrombus; this is consistent with other investigations, and is due to the increase in platelet-dependent thrombin production in hyperlipidemic patients. Also, platelet-dependent thrombin responds to statin treatment. In addition, hematopoietic cell-derived tissue factor is expressed during activation of coagulation, and the expression is enhanced in thrombosis in hyperlipidemic patients. Therefore, it seems reasonable to infer a correlation between dyslipidemia and in-stent thrombus.

The present multivariate analysis yielded results contrary to expectations: stent generation did not affect plaque YC grade or in-stent thrombus formation. Plaque YC grade was, however, affected by DM morbidity and by control of DM and HbA1c. This suggests that prevention of neoatherosclerosis and stent thrombosis after 2G- and 3G-DES implantation primarily depends not on choice of stent but on risk factor control. In conclusion, the higher NC grade and lower YC grade in 3G-DES than in 2G-DES might be associated with better long-term clinical outcome, which remains to be demonstrated in future studies.

Study Limitations

It is possible that the thrombus formation and YC grade of the plaque in the stented lesions were underestimated because the blood was cleared from only part of the vessel wall in the field of vision using dextran injection during CAS assessment of the stent. Additionally, CAS was not performed immediately after stent implantation. The initial YC grade of the stented site was therefore unknown.

Conclusions

The higher NC grade and lower YC grade in 3G-DES than in 2G-DES might be associated with better long-term clinical outcome, which remains to be determined in future studies.

Disclosures

The authors declare no conflicts of interest.

References


