Comparison of Chronic Angioscopic Findings of Bare Metal Stents, 1st-Generation Drug-Eluting Stents and 2nd-Generation Drug-Eluting Stents – Multicenter Study of Intra-Coronary Angioscopy After Stent (MICASA) –

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**Background:** No previous study has reported a comprehensive comparison of the chronic angioscopic findings after bare metal stent (BMS), and 1st- and 2nd-generation drug-eluting stents (DES).

**Methods and Results:** The Multicenter Study on Intra-Coronary Angioscopy after Stent (MICASA) is a multicenter registry of coronary angioscopy. A total of 264 stents were observed by coronary angioscopy 1 year after PCI. There were 15 BMS, 90 1st-generation DES, and 159 2nd-generation DES. Neointimal coverage (NC) of the stent was classified into 4 grades from 0 (no coverage) to 3 (complete coverage). Yellow color (YC) of plaque at the stented segment was graded from 0 (white) to 3 (bright yellow). Minimum (Min-) and Maximum (Max-) NC grade were significantly lower with 1st- and 2nd-generation DES than with BMS. Although the Max-NC grade was similar, the Min-NC grade was significantly higher for 2nd-generation DES than for 1st-generation DES. Both the YC grade and the incidence of thrombus with 2nd-generation DES were lower than with the 1st-generation DES and were comparable to BMS. Multivariate analysis showed that low-density lipoprotein, 1st-generation DES, and acute coronary syndrome were independent factors for yellow plaque (YG2 or 3), and that hypertension and 1st-generation DES were independent factors for the incidence of thrombus.

**Conclusions:** Coronary angioscopy revealed more homogeneous coverage with white neointima and less thrombus after 2nd-generation DES as compared with 1st-generation DES. These findings may explain the favorable clinical outcomes observed for patients treated with 2nd-generation DES.

**Key Words:** Bare metal stents; Coronary angioscopy; Drug-eluting stents

The drug-eluting stent (DES) has dramatically reduced the risk of restenosis and target vessel revascularization as compared with bare metal stents (BMS). Because the 1st-generation DES (1st-DES) was used widely around the world, concern was raised of an increased risk of late stent thrombosis after 1st-DES implantation. The 2nd-generation DES (2nd-DES) has been designed with the goal of improving safety, efficacy, and device performance. Several clinical studies have demonstrated that 2nd-DES are associated with favorable clinical outcomes, including lower incidence of very late stent thrombosis, than 1st-DES.

Coronary angioscopy permits direct visualization of the intracoronary structure. It has been demonstrated that coronary angioscopy is a useful tool for estimating the neointimal coverage (NC) of stent struts, not only quantitatively by showing the coverage grade but also qualitatively by showing the plaque’s yellow color (YC) grade. Several studies have compared the angioscopic findings of 2 specific types of stent, but no previous study has reported a comprehensive comparison of the chronic angioscopic findings for BMS, and 1st-DES and 2nd-DES. In this study, we performed a comprehensive comparison of the coronary angioscopic findings 1 year after implantation.
The outer section of the 4F probing catheter (USCI) was used as the guide for inserting the optical fiber into the coronary artery. The angioscopic observations were made while blood was removed from the view by injection of 3% dextan-40 through the probing catheter as previously reported. Angioscopy images were recorded on a digital recorder.

**Evaluation of the Angioscopic Findings**

We assessed NC of the stent struts, YC grade of plaque and the existence of thrombus. The degree of NC of the stent struts was classified into 4 grades as previously described (Figure 1).

In brief: grade 0=stent struts that were completely exposed (similar to immediately after implantation); grade 1=transparent stent struts with dull light reflection; grade 2=stent struts slightly visible, with no light reflection from stent struts; grade 3=stent struts completely covered, and not visible through the neointima.

YC under the stent was classified into 4 grades: 0 (white), 1 (light yellow), 2 (yellow) and 3 (bright yellow) (Figure 2). The maximum YC grade of the plaques was assessed. Angioscopic evaluations were made by specialists in coronary intervention and angioscopy who were blinded to the patient’s clinical status.

**Methods**

**Study Patients**

The Multicenter Study on Intra-Coronary Angioscopy after Stent (MICASA) is a multicenter registry of coronary angioscopy conducted in 4 Japanese institutions. A total of 264 stents were observed by coronary angioscopy 1 year after percutaneous coronary intervention. There were 15 lesions treated with BMS, 90 lesions with 1st-DES (64 lesions with sirolimus-eluting stent (SES), 26 lesions with paclitaxel-eluting stent (PES)), and 159 lesions with 2nd-DES (73 lesions with everolimus-eluting stent (EES), 56 lesions with zotarolimus-eluting stent, 30 lesions with biolimus-eluting stent). When more than 1 stent were used in 1 lesion, the same type of stent was exclusively used. We excluded patients in whom we could not obtain clear angioscopic imaging because of difficulty in removing blood from the view during angioscopic examination. We did not enroll patients with in-stent restenosis.

Informed consent was given by each patient and the study protocol was reviewed and approved by the ethics committee of each hospital.

**Angioscopic Examination**

Catheterization was performed with a radial, brachial or femoral approach using ≥6F catheters. After heparin administration, selective coronary angiography was performed. The coronary angioscopic examination was performed with the VFS-1300 angioscope (Nihon Kohden) and IF-783V optical fiber (Nihon Kohden). The outer section of the 4F probing catheter (USCI) was used as the guide for inserting the optical fiber into the coronary artery. The angioscopic observations were made while blood was removed from the view by injection of 3% dextan-40 through the probing catheter as previously reported. Angioscopy images were recorded on a digital recorder.

**Statistical Analysis**

Continuous and ordinal variables are shown as mean±SD.
We used the JMP statistical package (version 5.0.1 J, SAS Institute, Cary, NC, USA) for all statistical tests. A significance level of 0.05 was used and 2-tailed tests were applied. Student’s t-test and ANOVA were used for continuous variables, Wilcoxon test was used for ordinal variables. Categorical variables were expressed as frequencies and analyzed by chi-square statistics or Fisher’s exact test. Logistic regression analysis was performed to identify independent predictors of yellow plaque and thrombus. Yellow plaque was defined as YC grade 2 or 3.
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vs. 1.0 ± 0.8, P<0.001), larger heterogeneity index (1.7 ± 0.8 vs. 1.2 ± 0.8, P<0.001) and use of 1st-DES (61% vs. 25%, P<0.001). When patients were divided into ACS or stable angina pectoris (SAP) groups, similar findings were observed in both (Figures S1, S2).

Multivariate analysis showed that LDL (P=0.01), 1st-DES (P<0.0001), and ACS (P=0.006) were independent factors for yellow plaque, and that hypertension (P=0.04) and 1st-DES (P=0.002) were independent factors for thrombus.

Discussion

In this study, we compared the chronic angioscopic findings of BMS, 1st-DES and 2nd-DES. The main findings of this study were: (1) Max-NC and Min-NC grades with 1st- and 2nd-DES were lower than with BMS, (2) the Max-NC grade with 2nd-DES was similar to that with 1st-DES, but the Min-NC grade with 2nd-DES was higher, and (3) the heterogeneous index, YC grade and incidence of thrombus with 2nd-DES were all lower than with 1st-DES and were comparable to BMS.

Since their introduction in the early 2000s, DES have been widely used because of the dramatic decrease in in-stent restenosis and the need for target lesion revascularization. Instead, late stent failure, which includes late stent thrombosis and late catch-up phenomenon, were raised as a critical matter. Oversuppression of neointimal proliferation by the drugs and hypersensitivity to the polymers are thought to be responsible for late stent failure. The 2nd-DES were developed to overcome these disadvantages of 1st-DES, and have shown favorable clinical outcomes. In a meta-analysis of 51 randomized trials with ≥3 years’ follow-up of more than 50,000 patients, Palmerini et al demonstrated that 2nd-DES have substantially improved long-term safety and efficacy outcomes compared with 1st-DES.

The underlying mechanisms for late stent failure after DES have been investigated histologically and by intravascular imaging modalities. From the results of 81 autopsies of patients with 1st-DES, Finn et al showed that the ratio of uncovered to total stent struts and heterogeneity of healing

Results

Baseline Characteristics

The baseline clinical characteristics of each group are shown in the Table. Duration from stent implantation to coronary angioscopy of BMS, 1st-DES and 2nd-DES was 6.9±2.0 months, 7.8±2.1 months, and 10.0±2.8 months, respectively. Use of DES was associated with higher age, more females, smaller stent diameter, longer stent length, and dual antiplatelet therapy at the time of angioscopy.

Angioscopic Findings

The angioscopic findings of NC are shown in Figure 3. Max-NC and Min-NC grades were significantly lower for 1st-DES (2.2±0.7, P<0.001 for Max-NC; 0.5±0.6, P<0.001 for Min-NC) and 2nd-DES (2.1±0.7, P<0.001 for Max-NC; 1.0±0.8, P=0.01 for Min-NC) than for BMS (2.9±0.3 and 1.5±1.0, respectively). Although there was no significant difference in Max-NC grade, the Min-NC grade was significantly higher for 2nd-DES than for 1st-DES. The heterogeneity index was significantly smaller for 2nd-DES (1.1±0.7) than for 1st-DES (1.7±0.7, P<0.001), and comparable to that for BMS (1.4±1.0).

YC grade and incidence of thrombus are shown in Figure 4. YC grade was significantly higher with 1st-generation DES (1st-DES) than with BMS or 2nd-generation DES (2nd-DES). There was no significant difference in YC grade between BMS and 2nd-DES. The incidence of thrombus was lower with 2nd-DES than with 1st-DES, and was similar to BMS. BMS, bare metal stent; DES, drug-eluting stent.
Angioscopy of BMS, 1st- and 2nd-Generation DES

were predictors of late stent thrombosis. They also reported that neoatherosclerosis is a frequent finding with DES and occurs earlier than with BMS, suggesting another factor contributing to late stent failure. Intravascular imaging has been used to evaluate vascular responses to stents in living patients. Optical coherence tomography (OCT), as well as coronary angioscopy, is a useful imaging modality, because it has a 10-fold higher resolution than intravascular ultrasound. OCT permits qualitative assessment of NC, whereas the coverage grade by angioscopy is semiquantitative. However, angioscopy is the gold standard for detecting yellow plaque by full-color visualization and is superior to OCT for detecting intracoronary thrombus. Inoue et al compared the OCT and angioscopy findings for 26 coronary lesions at 10 months after SES implantation. They reported that the OCT-based definition of thrombus may underestimate the presence of subclinical thrombus detected by angioscopy.

In the current study using coronary angioscopy, we showed that the Min-NC grade, heterogeneity index and YC grade were associated with thrombus. A recent prospective study has demonstrated that yellow plaque at the lesion previously treated with DES predicts future late stent failure. Hypertension was negatively associated with thrombus, which was an unexpected finding, because most of the previous studies reported no association between hypertension and stent thrombosis. However, it is noteworthy that use of 1st-DES had the strongest association with thrombus.

Coronary angioscopy has been used to compare the vascular responses to different types of stent. Awata et al performed serial coronary angioscopic examinations after BMS and SES implantation. SES demonstrated lower NC grade, more intense yellow plaque and higher incidence of thrombus, while the BMS were completely covered by white neointima by 3–6 months. In another angioscopic study, PES showed the most heterogeneous neointimal formation and the highest incidence of neoatherosclerosis at one year after implantation of Endeavor and StentRestoration systems, and second-generation drug-eluting stents: a comprehensive comparison of the coronary angiographic findings of 1st-DES and 2nd-DES. These studies were, however, single-center studies with a sample size <100 patients. Using OCT, Choi et al reported that EES might have more favorable vascular responses after stent implantation than SES.

The current study is the first multicenter registry to perform a comprehensive comparison of the coronary angioscopic findings for BMS, 1st-DES and 2nd-DES. 1st-DES and 2nd-DES showed similar Max-NC grade, and a corresponding equivalent low incidence of in-stent restenosis. Min-NC was higher, and heterogeneous index and YC grade were lower with 2nd-DES than with 1st-DES, suggesting a relation to the lower incidence of thrombus with 2nd-DES. These angioscopic findings endorse the clinical efficacy of 2nd-DES similar to that for 1st-DES, and safety comparable to that of BMS.

Study Limitations

This was an observational study. Selection of stent depended on physicians and the baseline characteristics of each group were not matched. Reflecting market penetration, the number of BMS was small as compared with the number of DES. However, all consecutive patients undergoing coronary angiography of stent-implanted lesions were included. This registry enrolled only coronary angiographic examination 1 year after stent implantation, and serial changes in the angioscopic findings after stenting were not assessed. Because of the insurance regulations of Japan, other imaging modalities, including OCT and intravascular ultrasound, were not routinely used simultaneously. Finally, lack of a core laboratory was another limitation of this multicenter study. However, for the past 10 years, the MICASA group has held regular conferences (Chugoku-shikokum angioscopy conference) twice each year to reach consensus on coronary angiographic findings.

Conclusions

Coronary angioscopy revealed more homogeneous coverage with white neointima and less thrombus after 2nd-DES as compared with 1st-DES. These angioscopic findings endorse the clinical efficacy of 2nd-DES as similar to that of 1st-DES and a safety profile comparable to that of BMS. These findings may explain the favorable clinical outcomes of patients treated with 2nd-DES.

Acknowledgments

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Disclosures


References


Supplementary Files

*Figure S1.* Min-NC grade, Max-NC grade, heterogeneity index, YC grade and incidence of thrombus in stable angina pectoris (SAP) patients.

*Figure S2.* Min-NC grade, Max-NC grade, heterogeneity index, YC grade and incidence of thrombus in acute coronary syndrome (ACS) patients.

Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-16-0121