Angioscopic Comparison of Resolute and Endeavor Zotarolimus-Eluting Stents

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Background: Drug-eluting stents (DES) have reduced late loss and target lesion revascularization through the inhibition of neointimal hyperplasia, but instead increased the risk of very late stent failure due to incomplete neointimal coverage and neoatherosclerosis. Although newer DES are more effective and safer than the first-generation DES, the difference in the condition of the stented lesions between Resolute zotarolimus-eluting stents (R-ZES) and Endeavor zotarolimus-eluting stents (E-ZES) on angiography has not been reported.

Methods and Results: Consecutive patients who received R-ZES (n=46) or E-ZES (n=46) for de novo lesion of native coronary artery and had 1-year follow-up angiography were examined. Yellow color (grade 0–3), neointimal coverage (grade 0–2), heterogeneity score (maximum-minimum neointimal coverage grade) and thrombus (presence or absence) at stented lesion were evaluated. The maximum yellow color grade (1.2±0.9 vs. 0.7±1.0, P=0.005) was higher in R-ZES than in E-ZES. The maximum (1.9±0.3 vs. 1.5±0.5, P<0.001) and minimum (1.1±0.7 vs. 0.4±0.5, P<0.001) coverage grade was higher in E-ZES than in R-ZES. The heterogeneity score was higher in R-ZES than in E-ZES (1.0±0.5 vs. 0.7±0.7, P=0.007). Prevalence of thrombus was not different between the 2 stents (6.5% vs. 2.2%, P=0.4).

Conclusions: E-ZES had better neointimal coverage with less yellow plaque and lower heterogeneity score than R-ZES. The lesions with E-ZES appeared more stable than those with R-ZES. (Circ J 2016; 80: 650–656)

Key Words: Angioscopy; Drug-eluting stent (DES); Neointima; Thrombus; Vulnerable plaque

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Methods

At the stent-implanted segment at 1 year after implantation.

The 1-year follow-up catheterization was encouraged for all patients who received coronary intervention, but it was not performed when (1) the patient had renal dysfunction; or (2) informed consent was not obtained. In the 1-year follow-up catheterization, angioscopy was encouraged for all patients who received DES implantation, but it was not performed when (1) an angioscopy specialist was not available; (2) there was not adequate time for the examination; or (3) informed consent was not obtained. We have a registry of all patients who undergo angioscopy. From this registry, we retrospectively analyzed the consecutive patients who received R-ZES (between September 2012 and December 2013) or E-ZES (between May 2009 and July 2010) for de novo lesion of native coronary artery and had successful angioscopy at 1-year follow-up catheterization.

During this period, R-ZES was implanted in 198 patients and follow-up angioscopy was performed in 46 patients without reintervention before the follow-up; and E-ZES was implanted in 198 patients and follow-up angioscopy was performed in 46 patients without reintervention before the follow-up.
Angioscopy cannot differentiate the yellow plaque inside the
Results

Patient and Lesion Characteristics

The 46 patients (46 lesions) for R-ZES and 46 patients (49 lesions) for E-ZES comprised the study group. Follow-up interval was 389±41 days for R-ZES and 379±59 days for E-ZES. The patient, lesion, and procedural characteristics are listed in Tables 1. Representative R-ZES and E-ZES are shown in Figure 1.

Angioscopy

The maximum yellow color grade (1.2±0.9 vs. 0.7±1.0, P=0.005) was higher in R-ZES than in E-ZES (Figure 2A) for the whole study group. It was also higher in R-ZES than in E-ZES for ACS patients, while it was not different for non-ACS patients.

The maximum (1.9±0.3 vs. 1.5±0.5, P<0.001) and minimum (1.1±0.7 vs. 0.4±0.5, P<0.001) coverage grade was higher in E-ZES than in R-ZES (Figure 2B) for the whole study group. They were also higher in E-ZES than in R-ZES both for ACS patients and for non-ACS patients.

The heterogeneity score was higher in R-ZES than in E-ZES (1.0±0.5 vs. 0.7±0.7, P=0.007) for the whole study group. It was also higher in R-ZES than in E-ZES for the ACS patients (1.2±0.4 vs. 0.4±0.5, P=0.003), while it was not different for the non-ACS patients (1.0±0.6 vs. 0.8±0.7, P=0.3). Thrombus was detected only in 4 patients: 3 patients with R-ZES and 1 patient with E-ZES. Prevalence of thrombus was not different between R-ZES and E-ZES (6.5% vs. 2.2%.

Table 2. Lesion and Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n=95)</th>
<th>ACS (n=28)</th>
<th>Non-ACS (n=67)</th>
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</thead>
<tbody>
<tr>
<td>No. lesions</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Target vessel</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>LMT</td>
<td>46±2</td>
<td>49±2</td>
<td></td>
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<tr>
<td>LAD</td>
<td>21±6</td>
<td>20±4</td>
<td></td>
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<tr>
<td>LCX</td>
<td>1.2±0.2</td>
<td>1.2±0.2</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>13±2</td>
<td>21±4</td>
<td></td>
</tr>
<tr>
<td>IVUS use</td>
<td>46±40</td>
<td>49±10</td>
<td></td>
</tr>
<tr>
<td>No. stents</td>
<td>2±4</td>
<td>4±4</td>
<td></td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.0±0.3</td>
<td>3.0±0.3</td>
<td></td>
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<tr>
<td>Total stent length (mm)</td>
<td>2.7±0.4</td>
<td>2.7±0.4</td>
<td></td>
</tr>
<tr>
<td>Maximum balloon size (mm)</td>
<td>3.3±0.6</td>
<td>3.3±0.5</td>
<td></td>
</tr>
<tr>
<td>Maximum inflation pressure (atm)</td>
<td>13±3.4</td>
<td>17±4.3 &lt;0.001</td>
<td></td>
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</tbody>
</table>

QCA

Data given as mean±SD or n (%). IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; QCA, quantitative coronary angiography; RCA, right coronary artery. Other abbreviations as in Table 1.

Continuous data are given as mean±SD. Comparison of groups was done using unpaired Student’s t-test, chi-squared test, or Mann-Whitney test. Patient, lesion, and procedural characteristics were compared between R-ZES and E-ZES for the whole patient group, for ACS patients, and for non-ACS patients, respectively. To determine the contributing factors to maximum yellow color grade at 1 year, multivariate linear regression analysis was performed including stent type, stenting for ACS, gender, diabetes mellitus, hypertension, hypercholesterolemia, current smoking, chronic kidney disease, statin use, and eicosapentaenoic acid use as independent variables. P<0.05 was regarded as statistically significant. Statistical analysis was performed using SPSS (version 22.0J for Windows, SPSS, Chicago, IL, USA).

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neointima and that under stent in the original vessel wall, therefore we defined atherosclerosis as including both, given that both the yellow plaque formed after stent implantation and that in the native coronary artery are similarly associated with thrombus formation. If a yellow plaque in the original vessel wall is covered by a thick neointima, it becomes white and stable; but if the yellow plaque is covered by a thin neointima, it remains yellow and vulnerable. We therefore defined angioscopic neoatherosclerosis as the yellow plaque formed, or that with increased yellow color intensity, after stent implantation; that is, progression of atherosclerosis after stent implantation regardless of whether the yellow plaque exists in the neointima or in the original vessel wall.

Statistical Analysis

Continuous data are given as mean±SD. Comparison of groups was done using unpaired Student’s t-test, chi-squared test, or Mann-Whitney test. Patient, lesion, and procedural characteristics were compared between R-ZES and E-ZES for the whole patient group, for ACS patients, and for non-ACS patients, respectively. To determine the contributing factors to maximum yellow color grade at 1 year, multivariate linear regression analysis was performed including stent type, stenting for ACS, gender, diabetes mellitus, hypertension, hypercholesterolemia, current smoking, chronic kidney disease, statin use, and eicosapentaenoic acid use as independent variables. P<0.05 was regarded as statistically significant. Statistical analysis was performed using SPSS (version 22.0J for Windows, SPSS, Chicago, IL, USA).
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Angioscopy of R-ZES vs. E-ZES

Delayed Healing as a Cause of Late Stent Failure

In the first-generation DES, that is, Cypher sirolimus-eluting stents (C-SES) and Taxus paclitaxel-eluting stents (T-PES), the incidence of thrombus at follow-up was higher than that in bare metal stents (BMS).\(^1\)\(^2\)\(^3\)\(^4\)\(^5\) This delayed healing with high frequency of thrombogenesis has been regarded as 1 possible mechanism for thrombotic occlusion or stenosis progression, that is, stent failure, in DES. In the newer DES, however (eg, E-ZES and Xience everolimus-eluting stents [X-EES]), the incidence of thrombus at follow-up is very low.\(^2\)\(^3\)\(^4\)\(^5\) Both R-ZES and E-ZES had very low incidence of thrombus in the present study. Therefore, delayed healing would not be a major mechanism of late stent failure in those stents. Although heterogeneous neointima was associated with the presence of thrombus in the comparison of C-SES and T-PES used for stable angina patients,\(^1\)\(^6\) the incidence of thrombus in the present study was not significantly different between R-ZES and E-ZES, although the heterogeneity score was significantly higher in R-ZES than in E-ZES for the ACS patients. The

P=0.4) for the whole study group. The heterogeneity score was not different between the patients with and those without thrombus (1.3±1.0 vs. 0.9±0.6, P=0.4).

On multivariate linear regression analysis, stent type was the only significant contributing factor to maximum yellow color grade at 1 year among stent type, stenting for ACS, gender, diabetes mellitus, hypertension, hypercholesterolemia, current smoking, chronic kidney disease, statin use, and eicosapentaenoic acid use (Table 3).

Discussion

This is the first report to compare condition of the stented lesions between E-ZES and R-ZES on angioscopy at 1 year after implantation. We have shown in the present study that E-ZES had better neointimal coverage with less yellow plaque and lower heterogeneity score than R-ZES. Therefore, the coronary lesions with E-ZES appeared to have a more stable condition than those with R-ZES.

Figure 1. Representative case of (A–F) Resolute zotarolimus-eluting stent (R-ZES) and (G–L) Endeavor zotarolimus-eluting stent (E-ZES). (A) An 86-year-old male patient with effort angina had severe stenosis in the mid-right coronary artery and (B) received R-ZES. At (C) 1-year follow-up catheterization, no in-stent restenosis was seen on angiography, but (D–F) grade 2 yellow plaque and grade 1 neointimal coverage was detected on angioscopy. (G) A 71-year-old male patient with silent myocardial ischemia had severe stenosis in the mid-right coronary artery and (H) underwent implantation of E-ZES. At (I) 1-year follow-up catheterization, no in-stent restenosis was seen on angiography, and (J–L) complete neointimal coverage (grade 2) without yellow plaque was seen on angioscopy. Yellow line with arrows, site of stent implantation; yellow arrowhead, site of angioscopy.
Neoatherosclerosis as a Cause of Late Stent Failure

Progression of neoatherosclerosis has been reported as a cause of very late stent thrombosis and of restenosis after DES implantation. Higo et al reported that C-SES had poor neointimal coverage and accelerated the formation of yellow plaque at 10-month follow-up, with thrombus being more...
frequently detected in the newly formed yellow lesions. Histopathologically, Nakazawa et al. reported that the timing of atherosclerotic change, macrophage infiltration and/or necrotic core formation, was earlier in DES than in BMS. R-ZES had the higher incidence of yellow plaque at 1 year after implantation than E-ZES in the present study.

R-ZES vs. E-ZES
E-ZES is covered by thick non-atherosclerotic fibrous white neointima, similar to BMS, but has a higher incidence of neointima. According to the past clinical trials with long-term follow-up, R-ZES is covered by thick non-atherosclerotic fibrous white neointima, similar to BMS, but has a higher incidence of neointima. The principal difference in R-ZES vs. E-ZES as compared with E-ZES is its durable polymer coating (BioLinx Polymer System) with slower drug release kinetics. The drug release is slower in R-ZES (50% and 85% drug release at 7 and 60 days after stent implantation) than in E-ZES (75% drug release at 2 days). R-ZES has been found to have stronger suppression of neointimal hyperplasia with higher anti-restenotic efficacy than E-ZES in some clinical trials. In the short-term comparison between R-ZES and E-ZES, R-ZES had better suppression of neointimal hyperplasia but higher incidence of uncovered and malapposed struts at 6-month follow-up. According to the past clinical trials with long-term follow-up up to 5 years, TLR at 1 and 5 years were 3.9% and 10.2% in R-ZES, and 5.9% and 7.5% in E-ZES, respectively. Although these were not head-to-head comparison trials, the lesions with E-ZES appeared to be more stable during long-term follow-up than those with R-ZES.

Prediction of DES Failure on Angioscopy
We recently reported that in-stent atherosclerosis, as evaluated on the presence of yellow plaque at 1 year after the implantation of DES, is a risk factor for very late stent failure (in the Detect the Event of very late Stent failure from the drug-eluting stent NOT well covered by neointima determined on angioscopy [DESNOTE] study). Judging from this and the present result, R-ZES would have a higher risk of very late stent failure than E-ZES. In the DESNOTE study, the incidence of very late stent failure was 8.1% vs. 1.6% in the patients with vs. without yellow plaque (≥grade 2) during 4 years of follow-up. Yellow plaque (≥grade 2) was detected in 44% and 22% of the patients with R-ZES and E-ZES, respectively, in the present study. Therefore, the incidence of very late stent failure during 4 years of follow-up would be 4.5% vs. 3.0% in R-ZES vs. E-ZES, indicating that the difference would not be large enough to overcome the early difference of in-stent restenosis within 1 year, which was 4% vs. 13% in R-ZES vs. E-ZES. Very late stent failure, however, may not always be a benign event of restenosis but may be a life-threatening ACS. According to the DESNOTE study, very late stent failure may be prevented by the reduction of yellow plaque, for example with aggressive statin treatment; thus, aggressive statin treatment and other anti-atherosclerotic therapy should be more important after R-ZES implantation than after E-ZES implantation.

Study Limitations
The patient characteristics were generally similar but not completely matched between the R-ZES and E-ZES groups, because this was not a randomized trial. The R-ZES and E-ZES sample size was small, and selection bias may exist due to the fact that patients with renal dysfunction and those with small or tortuous coronary artery not suitable for angiography were not included in the present analysis.

Conclusions
E-ZES had better neointimal coverage with less yellow plaque and lower heterogeneity score than R-ZES at 1 year after implantation. The lesions with E-ZES appeared to be more stable than those with R-ZES.

Conflict of Interest / Financial Support
None.

References
1168—1174.


