Impact of Polymer Formulations on Neointimal Proliferation After Zotarolimus-Eluting Stent With Different Polymers Insights From the RESOLUTE Trial

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Background—Polymer formulation may affect the efficacy of drug-eluting stents. Resolute, Endeavor, and ZoMaxx are zotarolimus-eluting stents with different stent platforms and different polymer coatings and have been tested in clinical trials. The aim of this analysis was to compare the efficacy of zotarolimus-eluting stents with different polymers.

Methods and Results—Data were obtained from the first-in man trial or first randomized trials of each stent, The Clinical RESpOnse EvaLUation of the MedTronic Endeavor CR ABT-578 Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions (RESOLUTE), Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions (ENDEAVOR II), and ZoMaxx I trials. Follow-up intravascular ultrasound analyses (8 to 9 months of follow-up) were possible in 353 patients (Resolute: 88, Endeavor: 98, ZoMaxx: 82, Driver: 85). Volume index (volume/stent length) was obtained for vessel, stent, lumen, persistent plaque, and neointima. Cross-sectional narrowing was defined as neointimal area divided by stent area (%). Neointima-free frame ratio was calculated as the number of frames without intravascular ultrasound–detectable neointima divided by the total number of frames within the stent. At baseline, vessel, lumen, and persistent plaque volume index were not significantly different among the 4 stent groups. At follow-up, percent neointimal obstruction was significantly lower in Resolute compared with Endeavor, ZoMaxx, and Driver (Resolute: 3.7 ± 4.0, Endeavor: 17.5 ± 10.1, ZoMaxx: 14.6 ± 8.1, Driver: 29.4 ± 17.2%; P < 0.001). Greater maximum cross-sectional narrowing and higher neointima-free frame ratio, suggesting less neointimal coverage, were observed in Resolute compared with other stent groups. Multiple regression analysis confirmed that the biodurable polymer used in Resolute independently correlated with neointimal suppression among 3 zotarolimus-eluting stents.

Conclusions—The different polymer formulations significantly affect the relative amount of neointima for zotarolimus-eluting stents.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00248079.

Key Words: intravascular ultrasound • drug-eluting stent • coronary disease

Many types of drug-eluting stents (DES) have been developed and tested in human clinical trials and have shown significantly lower clinical and angiographic restenosis and target lesion revascularization compared with bare-metal stents. Each component of the DES—platform, drug, and polymer—contributes to acute and midterm results. Previous clinical studies have shown that the eluting property is one of the key factors that determines the efficacy of DES. In the Paclitaxel In-Stent Controlled Elution Study (PISCES), paclitaxel-eluting stents with different eluting properties were compared. In that trial, stents with longer drug elution (>30 days) showed significantly lower percent neointimal obstruction as compared with those with shorter drug elution (10 days) (8 ± 7% versus 17 ± 13%), suggesting an important role of formulation strategies for a given drug. However, this has not been fully evaluated in other DES.

We hypothesized that slow-release kinetic zotarolimus-eluting stents (ZES) may lead to reduced neointimal proliferation compared with fast-release ZES.

Clinical Perspective on p ●●●

Three clinical programs of evaluating ZES were tested in human clinical trials (Table 1). The Resolute ZES stent...
A newly developed biodurable polymer (C10/C19/PVP polymer) enables longer drug elution and a low-profile, thin-strut, stainless-steel–tantalum stent (TriMaxx, Abbott Vascular).7,8 The purpose of this study was to compare 3 ZESs and evaluate which factor or factors may have the most impact on neointimal suppression.

Methods

Patients

Data were derived from the The Clinical RESPOnse Evaluation of the Medtronic Endeavor CR ABT-578 Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions (RESOLUTE) trial for the Resolute stent,2,3 the Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE 578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions (ENDEAVOR II) trial for the Endeavor and Driver stents,4 and the ZoMaxx I trial for the ZoMaxx stent.7,8 The Resolute trial was the first-in-human, prospective, nonrandomized, multicenter study to test the safety and efficacy of the Resolute stent. The Endeavor II trial was a large-scale, prospective, randomized, double-blind, multicenter study to examine the safety and efficacy of the Endeavor stent as compared with the Driver. The ZoMaxx I trial was a prospective, randomized, single-blind, multicenter study to show the safety and efficacy of the ZoMaxx stent as compared with the Taxus Express2 stent. Major inclusion and exclusion criteria were similar among the 4 clinical trials. Target lesion was to be single, de novo native coronary lesion with a reference vessel diameter between 2.5 to 3.5 mm (2.25 to 3.5 mm in Endeavor II) and lesion length <27 mm (<30 mm in ZoMaxx I). The exclusion criteria were acute myocardial infarction within the past 72 hours, impaired left ventricular function with ejection fraction <30%, or lesions located within the left main coronary artery.

The study protocol for each clinical trial was approved by the institutional review board at each participating site, and consecutive, eligible patients signed written informed consent before the interventional procedure.

IVUS Procedure and Analysis

IVUS evaluation was planned for all subjects at prespecified enrollment sites at postprocedure and at 8 to 9 months after stent implantation regardless of symptom. All patients who were assigned to the IVUS cohort in each trial were enrolled in this study. In these trials, when baseline IVUS was unavailable for image analysis because of technical reasons, follow-up IVUS examination was still encouraged to obtain neointimal hyperplasia assessments as the primary IVUS end point of the study. The IVUS procedure was performed in a standard fashion using automated motorized pullback (0.5 mm/s) with commercially available imaging systems (40-MHz IVUS catheter, Boston Scientific Corp, Natick, MA, or 20-MHz IVUS catheter, Volcano Corp, Rancho Cordova, CA). IVUS analysis was done in an independent core laboratory at Stanford University Medical Center (Cardiovascular Core Analysis Laboratory, Stanford, CA).

Volumetric measurements were performed using PC-based software (echoPlaque, Indec Systems Inc, Santa Clara, CA) as previously described.9 Persistent plaque volume was calculated as vessel minus stent volume. Neointimal volume was calculated as stent minus lumen volume, and percent neointimal obstruction was defined as neointimal volume divided by stent volume. Each volume was divided by measurement stent length to adjust for different stent length (volume index: VI). Cross-sectional narrowing (CSN, %) was defined as neointima area divided by stent area. Neointima-free frame ratio (%) was calculated as the number of frames without IVUS-detectable neointima divided by the total number of frames within the stent.6 Tissue prolapse, stent edge dissection, and incomplete stent apposition (ISA) were assessed for qualitative IVUS analysis. ISA was identified as 1 or more struts clearly separated from the vessel wall with evidence of blood speckles behind the strut. ISA was classified as “persistent,” “resolved,” or “late-acquired,” as previous described.10 All images were reviewed by 2 independent observers, and adjudication of opinion was based on consensus of these observers.

Statistical Analysis

Statistical analysis was performed using Statview 5.0 (SAS Institute, Cary, NC). Continuous variables are expressed as mean±SD or median (interquartile range). For continuous variables, comparisons among 4 stents were performed with ANOVA, and comparisons between baseline and follow-up were done by 2-tailed, paired t test. In addition, repeated-measures ANOVA was performed to examine the interaction for stent types. Categorical variables were compared using χ². A probability value <0.05 was considered statistically significant. Multiple linear regression analysis was performed to examine the relationship between DES components and neointimal suppression.

Results

Study Population and Patient Characteristics

Follow-up IVUS analysis was available in 353 cases (Resolute: 88 cases, Endeavor: 98 cases, ZoMaxx: 82 cases, and Driver: 85 cases). Serial (baseline and follow-up) IVUS analysis was available in 277 cases (Resolute: 81 cases, Endeavor: 70 cases, ZoMaxx: 62 cases, and Driver: 64 cases). Patient and lesion characteristics were similar among the 4 groups except for diabetes and total stent length (Table 2). Follow-up duration was 271±31 days in RESOLUTE.

<table>
<thead>
<tr>
<th>Table 1. Comparison of ZES</th>
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<tbody>
<tr>
<td>Platform</td>
</tr>
<tr>
<td>Resolute</td>
</tr>
<tr>
<td>Endeavor</td>
</tr>
<tr>
<td>ZoMaxx</td>
</tr>
<tr>
<td>Drug (dose)</td>
</tr>
<tr>
<td>Zotarolimus (10 μg/mm)</td>
</tr>
<tr>
<td>Zotarolimus (10 μg/mm)</td>
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<tr>
<td>Zotarolimus (10 μg/mm)</td>
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<tr>
<td>Polymer</td>
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<tr>
<td>C10/C19/PVP polymer</td>
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<tr>
<td>Phosphorylcholine with</td>
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<tr>
<td>Phosphorylcholine with</td>
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<tr>
<td>Eluting time</td>
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<tr>
<td>60 d (85% of zotarolimus),</td>
</tr>
<tr>
<td>14 d (98% of zotarolimus)</td>
</tr>
<tr>
<td>30 d (90% of zotarolimus)</td>
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</tbody>
</table>

ZES indicates zotarolimus-eluting stents.
242±21 days in Endeavor, 272±18 days in ZoMaxx, and 240±25 days in Driver.

**Quantitative IVUS Analysis**

Quantitative IVUS analyses in in-stent segments are summarized in Table 3. There were no significant differences in vessel, lumen, peristent plaque volume, and minimum lumen area (MLA) at postprocedure among the 4 stent groups. Repeated-measures ANOVA analysis showed that there was a significant interaction between time course change of lumen VI/MLA and stent types. Delta lumen VI and delta MLA (late area loss) were significantly different between each 2-stent comparison except for Endeavor versus ZoMaxx. No significant volumetric changes from postprocedure to follow-up in vessel VI and peristent plaque VI were observed in any types of stent. The Resolute stent showed significantly larger MLA at follow-up and smaller late area loss compared with other stent groups.

Neointimal formations are summarized in Table 4. Resolute demonstrated a significantly lower percent neointimal obstruction compared with Endeavor, ZoMaxx, and Driver (Resolute: 3.7±4.0, Endeavor: 17.5±10.1, ZoMaxx: 14.6±8.1, and Driver: 29.4±17.2%; *P*<0.001). The statistical distribution of Resolute was shifted to the left (Figure 1) compared with other stent groups. Maximum CSN was significantly lower in Resolute compared with other stent groups, and the statistical distribution of Resolute was shifted to the left (Figure 2). Resolute showed significantly higher

### Table 2. Baseline Patient and Lesion Characteristics

|                        | Resolute (n=88) | Endeavor (n=98) | ZoMaxx (n=82) | Driver (n=85) | *P*
|------------------------|----------------|----------------|--------------|--------------|---
| Age, y                 | 61.3±10.3      | 59.6±10.7      | 60.6±11.7    | 59.1±10.4    | 0.516
| Male sex, %            | 69.3           | 83.7           | 76.8         | 78.8         | 0.133
| Hypertension, %        | 75.0           | 66.3           | 62.2         | 58.8         | 0.208
| Hyperlipidemia, %      | 93.2           | 83.7           | 84.1         | 82.4         | 0.150
| Diabetes mellitus, %   | 22.7           | 8.1            | 14.6         | 14.1         | 0.049
| Current smoker, %      | 21.6           | 24.5           | 19.5         | 29.4         | 0.249
| Unstable angina, %     | 29.5           | 34.8           | 38.9         | 32.1         | 0.690
| Target vessel, %       |                |                |              |              |<0.05
| LAD/LCX/RCA            | 32/24/44       | 42/24/34       | 45/27/28     | 45/23/32     | 0.387
| Lesion type >B2/C, %   | 81.8           | 75.3           | 74.4         | 77.4         | 0.650
| Average stent size, mm | 3.1±0.4        | 3.1±0.3        | 3.1±0.3      | 3.2±0.4      | 0.361
| Total stent length, mm | 21.9±4.7       | 23.7±7.2       | 21.2±5.7     | 23.1±6.3     | 0.028
| Reference diameter by QCA, mm | 2.8±0.4 | 2.8±0.5 | 2.8±0.4 | 2.8±0.5 | 0.569
| Lesion length by QCA, mm | 15.3±6.1    | 13.3±4.9       | 13.8±4.7     | 14.7±5.7     | 0.052

- LAD indicates left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; and QCA, quantitative coronary angiography.

### Table 3. Quantitative IVUS Analysis in In-Stent Segment

|                        | Resolute (n=81) | Endeavor (n=70) | ZoMaxx (n=62) | Driver (n=85) | ANOVA P
|------------------------|----------------|----------------|--------------|--------------|---
| Postprocedure          |                |                |              |              |<0.001<br>0.001<br><0.001<br>0.001
| Vessel VI, mm³/mm      | 15.1±4.0       | 16.1±3.8       | 14.5±3.7     | 15.3±4.0     | 0.256
| Lumen VI, mm³/mm       | 7.6±2.0        | 8.0±2.0        | 7.3±2.1      | 8.0±2.1      | 0.109
| Peristent plaque VI, mm³/mm | 7.4±2.5 | 8.1±2.5 | 7.4±2.2 | 7.3±2.6 | 0.488
| Stent VI, mm²/mm       | 7.7±2.0        | 8.1±2.0        | 7.3±2.1      | 8.0±2.1      | 0.118
| MLA, mm²              | 6.4±1.8        | 6.6±1.7        | 6.1±1.7      | 6.8±1.9      | 0.141
| Follow-up              |                |                |              |              |<0.001<br><0.001<br><0.001<br><0.001<br>0.001<br><0.001
| Vessel VI, mm³/mm      | 15.3±3.9       | 15.6±3.5       | 14.3±3.6     | 15.6±3.7     | 0.276
| Lumen VI, mm³/mm       | 7.4±1.9*       | 6.4±1.8*       | 6.1±1.9*     | 5.4±2.0*     | <0.001
| Peristent plaque VI, mm³/mm | 7.6±2.4 | 7.9±2.2 | 7.4±2.1 | 7.6±2.5 | 0.749
| MLA, mm²              | 6.0±1.7*       | 5.0±1.7*       | 4.6±1.7*     | 3.9±1.7*     | <0.001
| Late area loss, mm²    | 0.4±1.0        | 1.6±1.2        | 1.4±1.1      | 2.9±1.8      | <0.001

- Additional post hoc analysis showed that lumen VI at follow-up and MLA at follow-up were significantly larger in Resolute compared with Endeavor, ZoMaxx, or Driver and larger in Endeavor compared with Driver. Late area loss was significantly different between each 2-stent comparison except for Endeavor versus ZoMaxx. MLA indicates minimal lumen area; VI, volume index.
- *P*<0.05, postprocedure versus follow-up.
neointima-free frame ratio compared with other stent groups, suggesting less neointimal coverage compared with other stent groups.

**Multiple Regression Analysis**

To examine the relationship between DES components—drug, stent platform or polymer, and neointimal proliferation—multiple linear regression analysis was performed. After adjustment for variables with diabetes, hyperlipidemia, total stent length, stent area at postprocedure, and lumen area at distal reference, zotarolimus independently correlated with neointimal suppression among the 4 stent groups (standardized coefficient estimate: 0.565, \( P < 0.0001 \)) regardless of stent platform or polymer. In 3 ZES, several parameters showed independent correlations with neointimal suppression. Among those determinants, durable polymer was the strongest predictor to suppress neointimal hyperplasia regardless of stent platform (standardized coefficient estimate, 0.714; \( P < 0.0001 \); Table 5). However, the phosphorylcholine coating with topcoat did not independently correlate with neointimal suppression between Endeavor and ZoMaxx (standardized coefficient estimate, −0.145; \( P = 0.090 \)).

**Qualitative IVUS Analysis**

Table 6 summarizes the results of qualitative IVUS analysis including tissue prolapse, stent edge dissection, and incomplete stent apposition. There were no significant differences in tissue prolapse and stent edge dissection among the 4 stent groups. Regarding incomplete stent apposition, the incidence of resolved ISA and persistent ISA was similar among the 4 groups. However, late-acquired incomplete stent apposition was observed 6 cases (7%) in Resolute, whereas no incomplete stent apposition was observed in Endeavor, ZoMaxx, and Driver (\( P = 0.002 \)).

**Angiographic and Clinical Outcomes**

At 8- to 9-month follow-up, in-stent binary restenosis was 1.1% in Resolute, 8.6% in Endeavor, 6.4% in ZoMaxx, and 29.3% in Driver (\( P < 0.0001 \)). Target lesion revascularization at 1 year occurred at 1.1% in Resolute, 5.1% in Endeavor, 6.1% in ZoMaxx, and 9.4% in Driver (\( P = 0.119 \)).

![Figure 1. Statistical distribution of percent neointimal obstruction. Distribution of percent neointimal obstruction of the Resolute was shifted to the left, and average percent neointimal obstruction of the Resolute was significantly lower compared with the Endeavor, ZoMaxx, and Driver (\( P < 0.0001 \)).](image-url)
Discussion

The main findings of this IVUS analysis are as follows: (1) Resolute had a significantly smaller amount of neointima and less neointimal coverage compared with Endeavor, ZoMaxx, and Driver; (2) the biodurable polymer using in Resolute was independently correlated with neointimal suppression among 3 ZES; and (3) there was a higher incidence of late-acquired ISA in Resolute.

Impact of Drug Elution Time on Neointimal Suppression

Three types of ZES have been applied in humans: Resolute, Endeavor, and ZoMaxx and are summarized in Table 1. The only difference between Resolute and Endeavor stents is the polymer (biodurable polymer [slow release] versus phosphorylcholine coating [fast release]). The differences between the Endeavor and ZoMaxx stents are the polymer (phosphorylcholine coating with base coat [fast release] versus phosphorylcholine coating with base coat and topcoat [moderate release]) and the platform (Driver [cobalt-chromium alloy] versus TriMaxx [stainless steel and tantalum]). In terms of elution property, 98% of zotarolimus elutes within 14 days in Endeavor, 90% elutes within 30 days in ZoMaxx, and 85% of the drug elutes within 60 days and continue to elute up to 180 days in Resolute.

Although most DES with sirolimus analogs showed excellent suppression of neointimal hyperplasia (percent neointima obstruction <10%), the Endeavor ZES showed a relatively higher percent neointimal obstruction of 17% to 18%. In the present analysis, however, the Resolute ZES with a new biodurable polymer showed a much smaller percent neointimal obstruction of 3.7%. In terms of neointimal coverage, neointima-free frame ratio was negatively correlated with neointimal growth in this IVUS subanalysis. The neointima-free frame ratio was 53.3%, 13.2%, 14.6%, and 6.6% for Resolute, Endeavor, ZoMaxx, and Driver, respectively.

Table 5. Multiple Regression Analysis

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>95% Confidence Interval</th>
<th>Standardized Coefficient Estimate</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Driver-based platform</td>
<td>2.87</td>
<td>0.23 to 5.52</td>
<td>0.129</td>
<td>2.14</td>
<td>0.034</td>
</tr>
<tr>
<td>Durable polymer</td>
<td>-14.86</td>
<td>-17.33 to -12.40</td>
<td>-0.714</td>
<td>-11.87</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.37</td>
<td>0.48 to 6.3</td>
<td>0.119</td>
<td>2.30</td>
<td>0.023</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.41</td>
<td>-2.76 to 3.57</td>
<td>0.013</td>
<td>0.25</td>
<td>0.801</td>
</tr>
<tr>
<td>Total stent length</td>
<td>0.35</td>
<td>0.16 to 0.53</td>
<td>0.188</td>
<td>3.62</td>
<td>0.0004</td>
</tr>
<tr>
<td>Stent area at postprocedure</td>
<td>-0.23</td>
<td>-0.74 to 0.28</td>
<td>-0.047</td>
<td>-0.91</td>
<td>0.367</td>
</tr>
</tbody>
</table>
is the elution time (60 days versus 14 days), which is greater than the elution time difference between Endeavor and ZoMaxx (14 days versus 30 days). According to multiple regression analysis, zotarolimus is effective regardless of stent platform or polymer. In addition, our results suggest that slow release (60 days) was more effective in terms of neointimal suppression; however, fast- or moderate-release formulations (14 days and 30 days) were not associated with sufficient neointimal suppression. With these results, zotarolimus itself has a potent effect of neointimal suppression similar to other sirolimus analogs when the elution time is well controlled.

**Impact of Different Platform on Short-Term and Midterm Results**

Platform material and stent design significantly affect the short-term mechanical properties of metallic stents. Resolute and Endeavor ZES are composed of a thin, cobalt chromium alloy with an open-cell structure, whereas ZoMaxx ZES uses stainless steel and tantalum with an open-cell structure. Despite the difference in stent delivery systems, our IVUS analysis showed that there was no significant difference in terms of volumetric measurements at postprocedure including stent VI and minimum stent area as well as qualitative parameters including tissue prolapse, edge dissections, and baseline ISA.

As for midterm impact, the difference in stent platform was not correlated with neointimal suppression between Endeavor and ZoMaxx, which use the same drug and dosage and the similar polymer. Although our results do not compare thin struts versus thick struts, there is a concern over less radial strength in thin-strut, cobalt chromium stents compared with conventional thick-strut stent platforms. Further investigations may be required to confirm the stent platform performance including acute or chronic stent recoil, stent fracture, and nonuniform stent strut distribution.

**Late-Acquired ISA**

Late-acquired ISA has been reported to occur in 3% to 13% of sirolimus-eluting stents, 2% to 16% of paclitaxel-eluting stents, and 0% to 1% of Endeavor ZES. In this IVUS analysis, late-acquired ISA in Resolute was observed in 7% of the cases, which was significantly higher than Endeavor and ZoMaxx. Even in the same ZES family, the incidence of late-acquired ISA was different. Endeavor and ZoMaxx ZES with phosphorylcholine coating showed consistent results, whereas Resolute ZES with biodurable polymer showed relatively higher incidence of late-acquired ISA. Therefore a combination of zotarolimus and phosphorylcholine coating may not increase the development of late-acquired ISA. The difference in polymers appears to be a key factor in the development of late-acquired ISA rather than zotarolimus itself.

**Table 6. Qualitative IVUS Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Resolute (n=81)</th>
<th>Endeavor (n=70)</th>
<th>ZoMaxx (n=62)</th>
<th>Driver (n=64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue prolapse at postprocedure</td>
<td>19 (23.5%)</td>
<td>12 (17.1%)</td>
<td>13 (21.0%)</td>
<td>12 (18.8%)</td>
<td>0.736</td>
</tr>
<tr>
<td>Stent edge dissection at postprocedure</td>
<td>0/2</td>
<td>2/1</td>
<td>0/0</td>
<td>0/2</td>
<td>0.168</td>
</tr>
<tr>
<td>Proximal/distal, n</td>
<td>0/2</td>
<td>2/1</td>
<td>0/0</td>
<td>0/2</td>
<td>0.168</td>
</tr>
<tr>
<td>ISA Resolved ISA</td>
<td>4 (4.9%)</td>
<td>6 (8.6%)</td>
<td>5 (8.1%)</td>
<td>5 (7.8%)</td>
<td>0.831</td>
</tr>
<tr>
<td>Persistent ISA</td>
<td>13 (16.3%)</td>
<td>12 (17.1%)</td>
<td>7 (11.3%)</td>
<td>8 (12.5%)</td>
<td>0.726</td>
</tr>
<tr>
<td>Late-acquired ISA</td>
<td>6 (7.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

ISA indicates incomplete stent apposition.

**DES Components and Vessel Reactions**

Although stent platform, drug, and its carrier (polymer) are all important components of DES, the polymer plays an essential role to control local delivery of drugs. The present study represents the first lesion-level comparison of zotarolimus-family DES to primarily evaluate the impact of polymer difference on neointimal suppression. Indeed, the term “polymer difference” includes not only the difference in material and its biocompatibility but also pharmacokinetic differences in the tissue, such as the burst effect, the actual amount of drug released, the rate of drug release, the tissue levels of drug achievable for a given construct, local metabolic differences, and washout differences. Unfortunately, differential assessment of these factors would be virtually difficult in clinical studies. Similarly, several mechanical factors can also contribute to neointimal suppression, including differing levels of wall apposition for a given stent design, the amount of wall focal pressure exerted, and the degree of wall compaction achieved. These variables can affect the degree of transport of drug across the wall, the degree of wall stimulation leading to intimal thickening, and the degree of...
wall inflammation. In the current study, the same platform is used for all stents except for ZoMaxx. Stent expansion and incomplete stent apposition were also systematically evaluated and incorporated into the analysis. On the other hand, further detailed assessment of the above uncontrolled variables would require dedicated animal experiments.

The C10/C19/PVP polymer (BioLinx) used in Resolute has both hydrophilic and hydrophobic nature. The surface of the hydrophilic polymer has similar hydrophilicity characteristics to phosphorylcholine (PC), since many of the hydrophobic domains that interact with the drug and prolong drug elution time are internal to the polymer layer. In an in vitro test, C10/C19/PVP polymer and PC showed similar hydrophilicity evaluated by contact angle and monocyte adhesion to polymer surface, suggesting similar biocompatibility with PC.27

The current IVUS study was to test this hypothesis in clinical settings, but further studies with longer-term follow-up are required to determine whether the Resolute stents can show prolonged clinical safety similar to that observed in the Endeavor stents, owing to the similar characteristics of the C10/C19/PVP polymer to PC polymer on the surface.

Limitations

There are several limitations in this IVUS study. (1) The nonrandomized nature of the study with the limited number of patients may cause selection bias. However, differences in patient background were adjusted by multiple regression analysis. (2) Follow-up IVUS analysis was limited to a mid-term period of 8 to 9 months. Further studies with longer-term follow-up may be necessary for adequate assessment of safety. (3) Although we measured neointima-free ratio in this study, because of limited IVUS resolution (>80 μm axially and 200 μm laterally), endothelialization on the stent surface may not be fully visualized. (4) As an IVUS core analysis laboratory, we have a limited access to further detailed medical treatment information for all the investigated patients. However, the risk factor management was performed under the standard guidelines because the studied patients were all enrolled from controlled, prospective, clinical trials. (5) Underlying plaque compositional variables may affect drug uptake metabolism and the propensity for neointimal proliferation. Unfortunately, this evaluation was not possible in our trials, in which preintervention IVUS was not mandatory by protocol. Recently, an advanced radiofrequency-based tissue characterization technique became commercially available, and its use at preintervention may also be helpful in objective and quantitative assessment of plaque compositional variables.

Conclusions

The IVUS results from the present study demonstrated that Resolute ZES showed significantly lower neointimal growth and higher incidence of late-acquired ISA compared with other ZES. Different polymer formulations significantly affect the relative amount of neointima and the frequency of late-acquired ISA after placement of ZES.

Acknowledgments

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Disclosures

Dr Ormiston works as a consultant for Abbott Vascular. Drs Meredith and Fitzgerald work as consultants for Medtronic and Abbott Vascular.

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**CLINICAL PERSPECTIVE**

Each component of the drug-eluting stent (DES), platform, drug, and polymer, contributes to acute and mid-term results. In paclitaxel-eluting stents, it has been shown that polymer formulation may play a more important role than drug dose. In the PISCES trial, stents with longer elution (30 days) showed a significantly lower percent neointimal obstruction compared with those with shorter elution (10 days) (8.7% versus 17±13%), suggesting an important role of formulation strategies even for the same drugs. However, this has not been fully evaluated in other DESs. With respect to the zotarolimus-eluting stent (ZES), 3 clinical programs were tested in human clinical trials: Resolute, Endeavor, and ZoMaxx. The Resolute ZES system uses a newly developed biodurable polymer (C10/C19/PVP polymer; BioLinx), which enables longer drug elution and a low-profile thin-strut, cobalt-chromium alloy stent. The purpose of this study was to compare 3 ZESs and evaluate which factor or factors may have the most impact on neointimal suppression. At baseline, vessel, lumen, and persistent plaque VI were not significantly different among the 4 stents. At follow-up, percent neointimal obstruction was significantly lower in the Resolute compared with the Endeavor, ZoMaxx, and Driver trials (Resolute, 3.7±4.0; Endeavor, 17.5±10.1; ZoMaxx, 14.6±8.1; Driver, 29.4±17.2%). Pintima-free frame ratio, suggesting less neointimal coverage, were observed in the Resolute compared with other stent groups. Multiple regression analysis confirmed the biodurable polymer used in Resolute independently correlated with neointimal suppression among 3 ZESs. These findings confirmed that the different polymer formulations significantly affect the relative amount of neointima for ZES.
Impact of Polymer Formulations on Neointimal Proliferation After Zotarolimus-Eluting Stent With Different Polymers: Insights From the RESOLUTE Trial
Katsuhisa Waseda, Junya Ako, Masao Yamasaki, Tomomi Koizumi, Ryota Sakurai, Yoichiro Hongo, Bon-Kwon Koo, John Ormiston, Stephen G. Worthley, Robert J. Whitbourn, Darren L. Walters, Ian T. Meredith, Peter J. Fitzgerald and Yasuhiro Honda

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