Pathology of Second-Generation Everolimus-Eluting Stents Versus First-Generation Sirolimus- and Paclitaxel-Eluting Stents in Humans

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Background—Clinical trials have demonstrated that the second-generation cobalt-chromium everolimus-eluting stent (CoCr-EES) is superior to the first-generation paclitaxel-eluting stent (PES) and is noninferior or superior to the sirolimus-eluting stent (SES) in terms of safety and efficacy. It remains unclear whether vascular responses to CoCr-EES are different from those to SES and PES because the pathology of CoCr-EES has not been described in humans.

Methods and Results—A total of 204 lesions (SES=73; PES=85; CoCr-EES=46) from 149 autopsy cases with duration of implantation ≥30 days and ≤3 years were pathologically analyzed, and comparison of vascular responses was corrected for duration of implantation. The observed frequency of late and very late stent thrombosis was less in CoCr-EES (4%) versus SES (21%; P=0.029) and PES (26%; P=0.008). Neointimal thickness was comparable among the groups, whereas the percentage of uncovered struts was strikingly lower in CoCr-EES (median=2.6%) versus SES (18.0%; P<0.0005) and PES (18.7%; P<0.0005). CoCr-EES showed a lower inflammation score (with no hypersensitivity) and less fibrin deposition versus SES and PES. The observed frequency of neoatherosclerosis, however, did not differ significantly among the groups (CoCr-EES=29%; SES=35%; PES=19%). CoCr-EES had the least frequency of stent fracture (CoCr-EES=13%; SES=40%; PES=19%; P=0.007 for CoCr-EES versus SES), whereas fracture-related restenosis or thrombosis was comparable among the groups (CoCr-EES=6.5%; SES=5.5%; PES=1.2%).

Conclusions—CoCr-EES demonstrated greater strut coverage with less inflammation, less fibrin deposition, and less late and very late stent thrombosis compared with SES and PES in human autopsy analysis. Nevertheless, the observed frequencies of neoatherosclerosis and fracture-related adverse pathological events were comparable in these devices, indicating that careful long-term follow-up remains important even after CoCr-EES placement. (Circulation. 2014;129:211-223.)

Key Words: coronary restenosis ■ pathology ■ stents ■ thrombosis

Delayed arterial healing with poor strut coverage has been identified as the major substrate responsible for late and very late stent thrombosis (LST/VLST) after first-generation stainless steel sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) placement.1,2 Human autopsy studies have demonstrated that first-generation drug-eluting stents (DES) placed for “off-label” indications exhibit further delayed healing compared with those implanted for “on-label” indications.3,4 SES and PES show divergent mechanisms of LST/VLST: hypersensitivity reaction with diffuse extensive inflammation in the former versus malapposition with excessive fibrin deposition in the latter.4 In addition, in-stent neoatherosclerosis and stent fracture have emerged as other important contributing factors for late adverse events including LST/VLST and late target-lesion revascularization (TLR) after SES and PES placement. Neoatherosclerosis develops rapidly and more frequently within first-generation DES compared with bare metal stents (BMS).5 The incidence of stent fracture in first-generation DES has been reported to vary from 1.3% to 8.4% in clinical studies.6,7 However, in an autopsy study in which high-contrast film–based radiography was used, the prevalence of fracture was 29% in first-generation DES, in which grade V fracture was identified in 5% of the lesions and was associated with increased risk of restenosis and thrombosis.8

Clinical Perspective on p 223

The cobalt-chromium everolimus-eluting stent (CoCr-EES), a second-generation DES, consists of a thin (81 µm) strut platform coated with 7.8-µm-thick durable fluorinated copolymer and 1.0 µg/mm² everolimus.9 Pivotal randomized clinical trials have consistently demonstrated the superiority of CoCr-EES over PES in reducing stent thrombosis, myocardial infarction, and TLR up to 2 years of follow-up.10,11 On the other hand, randomized comparisons of CoCr-EES and SES have shown similar TLR rates between the devices, with a comparable or lower
Although a better safety profile of CoCr-EES versus SES has not been reported consistently in head-to-head randomized trials, recent large-scale registry data and meta-analysis of randomized trials have revealed that CoCr-EES shows substantially less stent thrombosis compared with SES and PES. Nevertheless, vascular responses to CoCr-EES versus SES and PES need further clarification because the pathology of CoCr-EES has not been reported in humans. Although clinical studies utilizing optical coherence tomography have reported better strut coverage in CoCr-EES versus SES and PES at 6 to 9 months after stent placement, detailed assessment of vascular responses to CoCr-EES, including the degree of inflammation, fibrin deposition, and strut coverage in relation to underlying plaque morphology, along with the mechanism(s) of stent thrombosis, can only be determined by histopathological studies. Moreover, the prevalence and characteristics of neointimal hyperplasia as well as the impact of stent fracture on adverse pathological outcomes in CoCr-EES remain to be elucidated. In the present study, we investigated pathological response to CoCr-EES compared with SES and PES in human coronary arteries using a registry database of autopsy cases.

Methods

Study Population

Between July 2002 and October 2012, the CVPath registry had received a total of 347 DES lesions with duration of implantation >30 days, which included 294 lesions with first-generation DES (SES [Cypher, Cordis Corp, Miami Lakes, FL] and PES [TAXUS Express or TAXUS Liberté, Boston Scientific; Natick, MA]) and 53 lesions with second-generation DES (zotarolimus-eluting stent [Endeavor or Resolute, Medtronic, Santa Rosa, CA] and CoCr-EES [XIENCE V, Abbott Vascular, Santa Clara, CA; or PROMUS, Boston Scientific]) from 220 autopsy cases. Of these, all available CoCr-EES (n=46 lesions) were included in the present study, and the maximum duration of implantation was 3 years (median=200 days; 25th to 75th percentiles, 121–360). For first-generation DES, 126 lesions in the last 3 years were excluded from the present analysis because of the longer duration of implantation (median=721 days; 25th to 75th percentiles, 361–1204) compared with CoCr-EES. Of the remaining 168 lesions in the first-generation DES, 10 lesions with duration of implantation >3 years were also excluded, and the remaining 158 lesions were included in the study (total SES=73 and PES=85 [63 SES and 79 PES were included in previous reports]). Consequently, a total of 204 DES lesions from 149 cases with similar duration of implantation (SES, PES, and CoCr-EES [>30 days, ≤3 years]) were evaluated in the present study. The present study did not include lesions with a platinum-chromium everolimus-eluting PROMUS Element stent (Boston Scientific) or a platinum-chromium everolimus-eluting PROMUS Element stent (Boston Scientific). Overlapping or consecutively implanted stents were treated as 1 lesion, whereas stents including a gap of >5 mm were considered to be separate lesions. All available clinical records were reviewed for patient history, duration of implantation, risk factors, and medications. Off-label indication was defined as stents deployed for acute myocardial infarction, bifurcation lesion, left main coronary artery, bypass graft, restenosis, chronic total occlusion, or lesion length >30 mm. Cause of death was reported as stent-related death, non–stent-related cardiovascular death, and noncardiac death, as described previously.1

Histological Preparation

Epicardial coronary arteries were dissected from the heart and radiographed with the use of high-contrast film–based radiography. Stented arteries were submitted for plastic embedding in methyl methacrylate. The entire stent was then sawed serially at 2- to 3-mm intervals. Histological sections were cut at 6 µm and stained with hematoxylin and eosin along with Movat pentachrome, as described previously.4

Pathological Assessment and Morphometric Analysis

The severity of calcification in the stented lesion was assessed on the basis of the radiographs as described previously: none, mild, moderate, and severe.4 Stent fracture was identified by assessment of high-contrast film–based radiographs and classified as grade I to V, where grade V fracture was defined as multiple strut fractures with acquired transection with gap in the stent body, as described previously.4 Acute stent thrombosis was defined as a platelet-rich thrombus occupying >30% of the cross-sectional area of the lumen, and stent restenosis was defined as >75% cross-sectional area narrowing by neointimal formation within the stented area, with or without atherosclerosis.8,10 Timing of the stent thrombosis was classified on the basis of the Academic Research Consortium definition as LST (31 days to 1 year) or VLST (>1 year). The underlying plaque morphology (outside stent struts) was classified with the use of traditional definitions of pathological intimal thickening, fibroatheroma, thin-cap fibroatheroma, plaque rupture, and fibrocalcific plaque.19 Newly formed atherosclerotic changes within the stent segment (neointimal hyperplasia) were classified into peri-strut foamy macrophage clusters, fibroatheroma, thin-cap fibroatheroma, and in-stent plaque rupture, as defined previously.1 Diffuse neointimal hyperplasia was characterized by involvement of >50% of stent length by foamy macrophages, fibroatheroma, thin-cap fibroatheroma, or rupture, and ≤50% involvement was defined as focal neointimal hyperplasia.

Morphometric analysis and histological assessment of coronary sections were performed as described previously.4 Morphometric measurements (IPLab, Scanalytics, Rockville, MD) included external elastic lamina, stent, and lumen areas, as well as the thickness above each strut. Uncovered struts were identified by the presence of platelet or fibrin thrombus or bare struts with absence of neointima and were reported as ratio of uncovered to total stent struts per section.1 Strut coverage was also evaluated on the basis of the presence or absence of >30% uncovered struts in at least 1 cross section, which has been shown to be a strong predictor of LST/VLST.1 The degree of fibrin deposition was evaluated as the percentage of struts with fibrin, and the severity of inflammation was assessed on the basis of a grading scale of 0 to 4 (score 0=<25% struts with ≤10 inflammatory cells; score 1=25% struts with ≤10 inflammatory cells; score 2=25–50% struts with >10 inflammatory cells; score 3=>50% struts with >10 inflammatory cells; score 4=>50% struts with >10 inflammatory cells; and score 5=2 strut-associated granulomatous inflammatory reactions). Hypersensitivity reaction was defined as diffuse circumferential inflammation predominantly consisting of T lymphocytes and eosinophils. The percentage of stent struts with giant cells and maximum number of eosinophils around each strut were also evaluated.1 In select cases, the Luna staining method was used to confirm the infiltration of eosinophils. Immunohistochemical staining was performed in select cases with the use of standard avidin-biotin techniques as described previously.1 Immunohistochemistry was performed for the identification of macrophages with the use of an anti-CD68 antibody (dilution 1:400; Dako, Carpinteria, CA), T lymphocytes with the use of an anti-CD45RO antibody (dilution 1:100; Dako), and B lymphocytes with the use of an anti-CD20 antibody (dilution 1:50; Dako).

Statistical Analysis

Results for continuous variables with normal distribution were expressed as mean±SD. Normality of distribution was tested with the Shapiro-Wilk test. Variables with nonnormal distribution were expressed as median and 25th to 75th percentiles. For per-patient analysis, comparisons of continuous variables with normal distribution were tested by 1-way ANOVA with Dunnett multiple-comparison correction, and categorical variables were analyzed by χ2 test with Bonferroni adjustment. These analyses were performed with the use of SPSS software version 19 (IBM Corporation, Armonk, NY). For per-lesion analysis, both linear regression and logistic regression were used as appropriate; corrections for intraclass correlations were applied, and robust variance estimates were employed. Bonferroni adjustment was used to account for multiple comparisons in these regression models. Dependent variables that did not pass the Shapiro-Wilk test for normality were transformed with generalized lognormal transformations before the regression analyses to de-skew the
### Table 1. Patient and Lesion Characteristics and Outcomes of DES

<table>
<thead>
<tr>
<th></th>
<th>SES</th>
<th>PES</th>
<th>CoCr-EES</th>
<th>P Value CoCr-EES vs SES</th>
<th>P Value CoCr-EES vs PES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td>n=56</td>
<td>n=61</td>
<td>n=32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>59±12</td>
<td>61±12</td>
<td>64±13</td>
<td>0.14</td>
<td>0.35</td>
</tr>
<tr>
<td>Male sex</td>
<td>41 (73)</td>
<td>46 (75)</td>
<td>20 (63)</td>
<td>0.29</td>
<td>0.19</td>
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<tr>
<td>Hypertension</td>
<td>28/39 (72)</td>
<td>39/48 (81)</td>
<td>19/30 (63)</td>
<td>0.45</td>
<td>0.078</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8/40 (20)</td>
<td>15/48 (31)</td>
<td>14/30 (47)</td>
<td>0.017</td>
<td>0.17</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>26/39 (67)</td>
<td>29/48 (60)</td>
<td>10/30 (33)</td>
<td>0.006</td>
<td>0.020</td>
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<tr>
<td>Previous MI</td>
<td>27/47 (57)</td>
<td>30/53 (57)</td>
<td>18/30 (60)</td>
<td>0.82</td>
<td>0.76</td>
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<tr>
<td>Previous CABG</td>
<td>10/53 (19)</td>
<td>12/57 (21)</td>
<td>10 (31)</td>
<td>0.19</td>
<td>0.28</td>
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<tr>
<td>Aspirin</td>
<td>21/28 (75)</td>
<td>30/40 (75)</td>
<td>4/6 (67)</td>
<td>0.67</td>
<td>0.66</td>
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<td>Thienopyridines</td>
<td>17/28 (61)</td>
<td>25/39 (64)</td>
<td>4/6 (67)</td>
<td>0.79</td>
<td>0.90</td>
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<td><strong>Cause of death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stent-related</td>
<td>14 (25)</td>
<td>20 (33)</td>
<td>5 (16)</td>
<td>0.30</td>
<td>0.076</td>
</tr>
<tr>
<td>Non-stent-related cardiac</td>
<td>20 (36)</td>
<td>24 (39)</td>
<td>15 (47)</td>
<td>0.30</td>
<td>0.48</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>18 (32)</td>
<td>15 (25)</td>
<td>11 (34)</td>
<td>0.83</td>
<td>0.32</td>
</tr>
<tr>
<td>Explant</td>
<td>4 (7)</td>
<td>2 (3)</td>
<td>1 (3)</td>
<td>0.43</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Lesion characteristics</strong></td>
<td>n=73</td>
<td>n=85</td>
<td>n=46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of implantation, d</td>
<td>270 (116–510)</td>
<td>210 (120–361)</td>
<td>200 (121–360)</td>
<td>0.75</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Indications for stenting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable CAD/ACS</td>
<td>42 (58)/31 (42)</td>
<td>56 (66)/29 (34)</td>
<td>27 (59)/19 (41)</td>
<td>0.92</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Lesion location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM/LAD/LCX/RCA/graft</td>
<td>1/27/20/24/1</td>
<td>3/37/17/21/7</td>
<td>2/17/11/15/5</td>
<td>0.36/Ref/0.78/0.51/0.078</td>
<td>0.69/Ref/0.46/0.79/0.57</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>22.0 (15.5–29.0)</td>
<td>21.0 (16.0–30.0)</td>
<td>22.0 (15.0–36.3)</td>
<td>0.71</td>
<td>0.62</td>
</tr>
<tr>
<td>Overlapping stents</td>
<td>23 (32)</td>
<td>26 (31)</td>
<td>17 (37)</td>
<td>0.59</td>
<td>0.50</td>
</tr>
<tr>
<td>With BMS</td>
<td>6 (8)</td>
<td>6 (7)</td>
<td>1 (2)</td>
<td>0.22</td>
<td>0.27</td>
</tr>
<tr>
<td>With same type of DES</td>
<td>14 (19)</td>
<td>17 (20)</td>
<td>10 (22)</td>
<td>0.74</td>
<td>0.82</td>
</tr>
<tr>
<td>With different type of DES</td>
<td>4 (5)</td>
<td>4 (5)</td>
<td>9 (20)</td>
<td>0.057</td>
<td>0.032</td>
</tr>
<tr>
<td>Bifurcation multistenting</td>
<td>7 (10)</td>
<td>15 (18)</td>
<td>2 (4)</td>
<td>0.31</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>No. of stents per lesion</strong></td>
<td>1.4±0.8</td>
<td>1.4±0.7</td>
<td>1.6±1.0</td>
<td>0.37</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Underlying plaque morphology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rupture TCFA/fibroatheroma/FC/PIT/others†</td>
<td>25/28/8/7/5</td>
<td>20/42/11/8/4</td>
<td>11/19/5/4/7</td>
<td>0.37/Ref/0.91/0.83/0.37</td>
<td>0.70/Ref/0.99/0.88/0.060</td>
</tr>
<tr>
<td><strong>Lesion calcification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/mild/moderate/severe</td>
<td>16/28/15/14</td>
<td>20/38/19/8</td>
<td>6/22/7/11</td>
<td>0.57</td>
<td>0.15</td>
</tr>
<tr>
<td>Off-label indication</td>
<td>41 (56)</td>
<td>48 (56)</td>
<td>24 (52)</td>
<td>0.71</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Stent outcome‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis (late and very late)</td>
<td>15 (21)</td>
<td>22 (26)</td>
<td>2 (4)</td>
<td>0.029</td>
<td>0.008</td>
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<tr>
<td>Late stent thrombosis</td>
<td>7/40 (18)</td>
<td>17/64 (27)</td>
<td>2/36 (6)</td>
<td>0.39</td>
<td>0.031</td>
</tr>
<tr>
<td>Very late stent thrombosis§</td>
<td>8/33 (24)</td>
<td>5/21 (24)</td>
<td>0/10 (0)</td>
<td>&lt;0.0005</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Restenosis</td>
<td>10 (14)</td>
<td>10 (12)</td>
<td>18 (17)</td>
<td>0.63</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD, median (25th to 75th percentiles), or n (%), unless otherwise specified. All tests at the level of the lesions use either logistic regression or linear regression with correction for intraclass correlations among lesions and robust variance estimates, after appropriate de-skewing transformations in the case of interval-dependent variables. Ordered dependent variables, such as number of stents per lesion, are treated with ordered logistic regression. ACS indicates acute coronary syndromes; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CoCr-EES, cobalt-chromium everolimus-eluting stent; DES, drug-eluting stent; FC, fibrocalcific plaque; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LM, left main coronary artery; MI, myocardial infarction; RCA, right coronary artery; PES, paclitaxel-eluting stent; PIT, pathological intimal thickening; Ref, reference category; SES, sirolimus-eluting stent; and TCFA, thin-cap fibroatheroma.

*Multiple P values refer to each category in the order given. The second category serves as the reference category in a multinomial logistic regression for each of the 5 categories in lesion location and underlying plaque morphology. Because each of these 2 dependent variables involves 8 tests each, multiple-comparisons protection via the Bonferroni method requires that no P value be considered significant unless P<0.05/8=0.00625. In all other cases, the Bonferroni criterion for significance is P<0.05/2=0.025.

†Others include nodular calcification and restenotic lesions.

‡Only these dependent variables were corrected with the covariate duration of implantation because the other lesion variables in this table do not reflect vascular healing response, and therefore they are not associated with duration of implantation.

§For very late stent thrombosis, Poisson regression (with the same conditions, eg, duration of implantation as covariate and robust variance estimate) was used instead of logistic regression because the use of the CoCr-EES perfectly predicts no very late stent thrombosis, and logistic regression yields no confidence estimate under this condition.
distribution of errors in the variables. Ordered dependent variables, such as number of stents per lesion, were treated with ordered logistic regression analysis. Lesion location, underlying plaque morphology, and distribution of neatherosclerosis involved multiple categorical variables; a multinomial logistic regression was employed for the analysis. Fisher exact test or Poisson regression substituted for logistic regression analysis when regression failed because of a low observed frequency. Even though there were no significant differences in duration of implantation among the 3 groups, to ensure that the impact of duration of implantation was accounted for, all regression analyses of dependent variables with regard to vascular responses (ie, stent outcome, morphometric analysis, and prevalence of neatherosclerosis and stent fractures) included duration of implantation as an independent covariate, whether or not this correction was statistically significant. The tests at the level of the lesions were performed with STATA 9.2 (StataCorp LP, College Station, TX). All tests were 2-tailed, and the analyses with Bonferroni adjustment required $P<0.025$ (0.05 divided by 2) for statistical significance except when multiple categorical variables were involved, in which case the appropriate divisor of the nominal $\alpha$ value (threshold of significance for a $P$ value) of 0.05 was noted in the footnotes. A value of $P<0.05$ was considered significant for ANOVA with Dunnett correction.

**Results**

**Patient and Lesion Characteristics and Outcome of DES**

There were no differences in clinical characteristics between CoCr-EES and first-generation DES (Table 1). Risk factors were similar between different stents except that CoCr-EES had greater prevalence of diabetes mellitus than SES, and hyperlipidemia was less frequent in CoCr-EES compared with

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Representative images of sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), and cobalt-chromium everolimus-eluting stent (CoCr-EES) implanted for stable coronary artery disease (CAD; **A**: a to f) and for acute coronary syndromes (ACS; **B**: g to l). a and b, Histological sections from a 53-year-old man with SES implanted in the proximal left anterior descending coronary artery for 13 months. A low-power image (a) shows mild neointimal growth and underlying fibrocalcific plaque. Focal uncovered struts are highlighted in a high-power image in b. *Stent strut. c and d, Histological sections from a 71-year-old man with PES implanted in the right coronary artery 11 months antemortem. A low-power image (c) shows mild to moderate neointimal proliferation and underlying fibroatheroma. Note uncovered struts with persistent peri-strut fibrin deposition shown at high-power image in d. e and f, Histological sections from a 60-year-old man who received CoCr-EES in the mid left circumflex artery 6 months antemortem. A low-power image (e) shows mild neointimal proliferation and underlying fibrocalcific plaque. All struts are covered with proteoglycan-rich neointima with absence of fibrin, which is highlighted in a high-power image in f. g and h, Histological sections from a 74-year-old woman who received SES in the proximal left anterior descending coronary artery for acute myocardial infarction 18 months antemortem, who died of diffuse severe coronary artery disease. A low-power image (g) shows mild neointimal proliferation. Note focal uncovered struts and strut penetration into the necrotic core (NC; h). i and j, Histological sections from a 64-year-old woman with PES implanted in the right coronary artery for acute myocardial infarction 9 months antemortem, who died of congestive heart failure. A low-power image (i) shows patent lumen with stent struts surrounded by fibrin and an underlying NC. Note uncovered struts with fibrin deposition that overlie the NC (j). k and l, Histological sections from a 67-year-old man who received CoCr-EES in the proximal left anterior descending coronary artery for non-ST-segment elevation acute myocardial infarction 5 months antemortem, who died of noncardiac causes. A low-power image (k) shows mild neointimal proliferation and an underlying large NC. All struts are covered with a thin neointima overlaying the NC, which is highlighted in the high-power image in l. All histological sections are stained with Movat pentachrome. DES indicates drug-eluting stents.
SES and PES. The duration of implantation in all groups was similar, and lesion characteristics were comparable among the groups (Table 1). Representative histological images of SES, PES, and CoCr-EES implanted for stable coronary artery disease and for acute coronary syndromes are shown in Figure 1.

The observed frequency of LST and VLST within the study population was less in CoCr-EES (4%) compared with SES (21%; \(P=0.029\)) and PES (26%; \(P=0.008\); after adjustment for duration of implantation; Table 1). There were 2 lesions with CoCr-EES showing LST, and no VLST was observed in CoCr-EES. Both of the lesions with LST in the CoCr-EES group had CoCr-EES implanted over an underlying PES implant. Pathological etiologies for the 2 LST in CoCr-EES were identified as uncovered struts associated with overlapping stents and neointimal erosion with restenosis, respectively (Figure 2). The prevalence of restenosis observed for CoCr-EES (17%) did not differ significantly from that observed for SES (14%) and PES (12%).

**Morphometric Analysis**

Morphometric analysis was performed on a total of 1357 histological sections (SES=479; PES=578; CoCr-EES=300) with 14456 struts (SES=4546; PES=6037; CoCr-EES=3873; Table 2). Areas of external elastic lamina, stents, and underlying plaques were observed to be smaller in CoCr-EES compared with SES and PES, in which case the difference in external elastic lamina area between the CoCr-EES and the SES groups was statistically significant (\(P=0.010\)). The mean and maximum neointimal thicknesses in CoCr-EES did not differ significantly from those in SES and PES (Table 2). On the contrary, the observed frequency of uncovered struts was strikingly lower in CoCr-EES (median=2.6%; 25th to 75th percentiles, 0–7.1) compared with SES (18.0%; 25th to 75th percentiles, 0–51.4; \(P<0.0005\)) and PES (18.7%; 25th to 75th percentiles, 7.1–44.4; \(P<0.0005\)). The prevalence of DES lesions with >30% uncovered struts was also significantly lower in CoCr-EES (20%) than in SES (60%; \(P<0.0005\)) and PES (67%; \(P<0.0005\)).

The maximum neointimal thickness and the prevalence of DES with >30% uncovered struts in CoCr-EES versus SES or PES were further compared on the basis of stratified duration of implantation (Figure 3). All DES showed a progressive increase in the maximum neointimal thickness and a gradual decrease in the prevalence of DES lesions with >30% uncovered struts as the duration of implantation increased. The maximum neointimal thickness did not differ significantly between the groups within each period of the duration of implantation. In contrast, the prevalence of lesions with >30% uncovered struts in CoCr-EES was lower than that in SES and PES at each duration of implantation; the differences between the groups were statistically significant for 3 to 9 months (for CoCr-EES versus PES) and 9 to 36 months (for CoCr-EES versus both SES and PES; Figure 3).

**Figure 2.** Late stent thrombosis in 2 cases with cobalt-chromium everolimus-eluting stent (CoCr-EES). A and B, Histological sections from a 55-year-old man with CoCr-EES implanted over an underlying paclitaxel-eluting stent (PES) in the proximal right coronary artery 6 months antemortem, who died suddenly of stent thrombosis. A low-power image (A) shows occlusive luminal thrombus (Thr) within the stents with underlying calcified plaque; Ca indicates calcification. A few struts of CoCr-EES are covered with thin neointima, but the majority of the struts are uncovered, which is highlighted in a high-power image in B. C and D, Histological sections from a 72-year-old woman with CoCr-EES implanted over an underlying PES in the proximal left anterior descending coronary artery 7 months antemortem. The patient presented with acute myocardial infarction from stent thrombosis and underwent balloon angioplasty, which resulted in rupture of the left anterior descending coronary artery. A low-power image (C) shows in-stent restenosis with luminal thrombus; the neointima is focally dissected because of the balloon angioplasty with overlying nonocclusive thrombus. A high-power image (D) shows erosive neointima with overlying fibrin and platelet thrombus. A and B are stained with Movat pentachrome, and C and D are stained with hematoxylin and eosin.
Further subgroup analysis demonstrated that the superiority of CoCr-EES over SES and PES in terms of lower prevalence of >30% uncovered struts was consistently observed irrespective of age, sex, indications for stenting (stable coronary artery disease versus acute coronary syndromes and on- versus off-label), and lesion characteristics including lesion location, stent length, stent diameter, single or multiple stenting, underlying plaque morphology (stable versus unstable plaques), and the degree of lesion calcification (Figure 4). Stent struts with fibrin deposition were significantly less in CoCr-EES (8.5%; 25th to 75th percentiles, 0–28.2) compared with SES (29.9%; 25th to 75th percentiles, 12.1–59.9; P=0.001) and PES (51.1%; 25th to 75th percentiles, 36.9–72.9; P<0.0005; Table 2). CoCr-EES showed significantly lower inflammation scores (0.26; 25th to 75th percentiles, 0–0.60) compared with SES (1.00; 25th to 75th percentiles, 0.33–2.00; P<0.0005) and PES (1.00; 25th to 75th percentiles, 0.13–1.44; P=0.006). Eosinophil infiltration and giant cell reaction were also significantly less in CoCr-EES compared with SES; however, CoCr-EES showed greater giant cell reaction compared with PES. The observed frequency of malapposition was lower in CoCr-EES (4%) compared with SES (16%) and PES (18%), although the differences were not statistically significant. No hypersensitivity reaction was observed in CoCr-EES, whereas 8% of SES (6 of 73) showed hypersensitivity. One patient had received 2 SES implants and 1 CoCr-EES implant; both of the SES showed diffuse hypersensitivity reaction, and 1 of them had occlusive thrombus, whereas the CoCr-EES showed only focal inflammation with eosinophils and T lymphocytes without hypersensitivity reaction (Figure 5A). A total of 4 lesions (8.7%) had focal eosinophil infiltration (>10 per strut) with T lymphocytes in CoCr-EES (Figure 5B).

<table>
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<td>TCFA/in-stent plaque rupture§</td>
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<tr>
<td>Distribution of neoatherosclerosis¶</td>
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<td>Prevalence of calcification within the neointima║</td>
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Values are expressed as mean±SD, median (25th to 75th percentiles), or n (%), unless otherwise specified. All regression analyses were corrected with the covariate duration of implantation. Multiple-comparison thresholds were used as in Table 1. CoCr-EES indicates cobalt-chromium everolimus-eluting stent; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; and TCFA, thin-cap fibroatheroma.

*Prevalence of drug-eluting stent lesion with >30% uncovered struts in ≥1 cross section.†
†Using ordered logistic regression on 16 cuts in counts dominated by 0 because no transformation justified linear regression. This retained robust variance estimates and correction for intraclass correlations among lesions.
‡Using Poisson regression for these counts.
§Tabular Fisher exact test substituted for regression because regression fails in cases in which CoCr-EES perfectly predicts absence of hypersensitivity reaction and TCFA/in-stent plaque rupture vs SES.
║Evaluated on drug-eluting stent implanted in native coronary arteries.
¶Using multinomial logistic regression with None as the reference.
Prevalence and Characteristics of Neoatherosclerosis

The overall prevalence of neoatherosclerosis after CoCr-EES implantation in native coronary arteries was 29%, which did not differ significantly from SES (35%) and PES (19%; Table 2). There was no significant difference in the observed frequency of each characteristic of neoatherosclerosis (foamy macrophage clusters, fibroatheroma, and thin-cap fibroatheroma) between SES, PES, and CoCr-EES. The prevalence of >30% uncovered struts at 1, 3, and 9 months was 13%, 16%, and 16%, respectively, for SES, 23%, 19%, and 19% for PES, and 16%, 17%, and 17% for CoCr-EES (Figure 4). The multivariate analysis showed that the duration of implantation was a significant predictor of >30% uncovered struts (p = 0.001 for CoCr-EES vs SES and p = 0.005 for CoCr-EES vs PES, Table 1).

Figure 3. Box-and-whisker plots showing maximum neointimal thickness (A) and bar graphs showing prevalence of drug-eluting stent (DES) lesions with >30% uncovered struts (B) stratified by duration of implantation in sirolimus-eluting stents (SES), paclitaxel-eluting stents (PES), and cobalt-chromium everolimus-eluting stents (CoCr-EES). In box-and-whisker plots, lines within boxes represent median values; the upper and lower lines of the boxes represent the 75th and 25th percentiles, respectively; the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively. P values for CoCr-EES vs SES and for CoCr-EES vs PES are presented. Multiple-comparison threshold is used as in Table 1.

Figure 4. Subgroup analysis for the presence of >30% uncovered struts in cobalt-chromium everolimus-eluting stents (CoCr-EES) vs sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). All regression analyses include duration of implantation as a covariate. Multiple-comparison threshold is used as in Table 1. *Underlying stable plaques include fibroatheroma, fibrocalcific plaque, nodular calcification, pathological intimal thickening, and restenotic lesions. ACS indicates acute coronary syndromes; CI, confidence interval; LAD, left anterior descending coronary artery; OR, odds ratio; and TCFA, thin-cap fibroatheroma.
fibroatheroma or in-stent plaque rupture) between the groups; however, a dominant morphology in CoCr-EES and PES was foamy macrophage clusters (CoCr-EES=67% [8 of 12]; PES=87% [13 of 15]) which was less frequent in SES (32% [8 of 25]). No unstable features of neatherosclerosis (thin-cap fibroatheroma or plaque rupture) were observed in CoCr-EES. Diffuse nature of neatherosclerotic change was observed in 42% (5 of 12) of CoCr-EES with neatherosclerosis, which was not significantly different from SES (60% [15 of 25]) and PES (27% [4 of 15]). The earliest duration of implantation showing neatherosclerosis in CoCr-EES within the native coronary arteries was 270 days, which was relatively longer than that in SES (120 days) and PES (70 days). Representative images of neatherosclerosis in CoCr-EES implanted in native coronary arteries are shown in Figure 6.

Prevalence of Stent Fracture and Fracture-Related Complications

The overall observed frequency of stent fracture in CoCr-EES was 13%, which was significantly lower than SES (40%; P=0.007) but was comparable to PES (19%; P=0.45; Figure 7A). The observed frequency of grade V fracture of CoCr-EES (2.2%) did not differ from SES (6.9%; P=0.26) and PES (2.4%; P=0.96). Moreover, there was no significant difference in fracture-related adverse pathological events (restenosis or thrombosis) of CoCr-EES (6.5% [n=3 restenosis]) versus SES (5.5% [n=4: 2 restenosis and 2 thrombosis]; P=0.83) and PES (1.2% [n=1 thrombosis]; P=0.16). The 6 lesions (5 patients) showing CoCr-EES fracture are listed in Table 3. The majority of the CoCr-EES fractures were identified in the middle, adjacent to the hairpin bend in the nonlinear

Figure 5. Hypersensitivity reaction in sirolimus-eluting stents (SES) vs focal inflammation in cobalt-chromium everolimus-eluting stents (CoCr-EES). A, Histological sections from a 58-year-old man with 2 SES and 1 CoCr-EES, who died suddenly 1 day after nasal polyp surgery. Dual antiplatelet therapy was stopped 5 days before the surgery. a and b, SES implanted in distal right coronary artery (RCA; a) and in the mid left circumflex artery (LCX; b) for 3 years. Radiographs show SES with (a-1) and without (b-1) underlying severe calcification, with no stent fracture. A low-power histology image in a-2 (Movat) shows occlusive platelet-rich thrombus (Thr) with transmural inflammation and extensive malapposition of stent struts with fibrin deposition (double arrows). A low-power image in b-2 shows mild neointimal proliferation with transmural inflammation but no luminal thrombus. High-power images (a-3 to a-6 and b-3 to b-6) show extensive inflammation predominantly consisting of eosinophils (Luna stain [a-4 and b-4]) and T lymphocytes (CD45RO [a-5 and b-5]) but rare B lymphocytes (CD20 [a-6 and b-6]). c, A CoCr-EES implanted in the proximal RCA of 7-month duration. A radiograph (c-1) shows a stent with underlying severe calcification and no fracture. A low-power histology image (c-2) shows a patent lumen with thin neointima. High-power images (c-3 to c-6) show focal mild inflammation consisting of eosinophils (c-4 and T lymphocytes (c-5) but no B-lymphocytes (c-6). B, Histological sections from a 51-year-old man who received CoCr-EES in the distal LCX 4 months antemortem. A low-power image (d) (hematoxylin and eosin stain) shows a patent lumen with mild neointimal proliferation and underlying calcified plaque. High-power images (e to h) show focal inflammation within the neoaintima consisting of eosinophils (f) and T lymphocytes (g), but no B lymphocytes were observed (h). *Stent strut.
Discussion

The principal findings of the present autopsy study are as follows: (1) CoCr-EES showed a lower frequency of LST/VLST with fewer uncovered struts, less inflammation (with no hypersensitivity), and less fibrin deposition compared with SES and PES in humans; (2) greater strut coverage in CoCr-EES versus SES and PES was consistently identified irrespective of lesion characteristics and indications for stenting; (3) neointimal thickness in CoCr-EES was similar to that in SES and PES and progressively increased with time; (4) CoCr-EES showed the presence of neoatherosclerosis, the frequency of which was comparable to that in SES and PES; and (5) overall stent fracture was less frequent in CoCr-EES versus SES and PES regardless of lesion characteristics, which is in agreement with several registry-based studies and a pooled analysis from randomized clinical trials showing the safety and efficacy of CoCr-EES versus first-generation DES in patients with acute coronary syndromes, long or small-vessel lesions, and unprotected left main coronary disease.22–25 A recent randomized comparison of CoCr-EES and BMS in patients with ST-segment elevation acute myocardial infarction showed a significantly lower incidence of TLR and stent thrombosis in CoCr-EES versus BMS at 1 year after stent implantation.26

Poor strut coverage has been shown to be the best predictor of LST/VLST after first-generation DES placement.1 In this regard, fewer uncovered struts in CoCr-EES likely contributed to a lower frequency of LST/VLST, which could be associated with improved DES components. In vivo and ex vivo experimental studies have shown that thin stent struts are associated with less flow disturbance, greater endothelial cell coverage, and less thrombogenicity compared with thick stent struts.20,21 Fluorinated copolymer of CoCr-EES consists of vinylidene fluoride and hexafluoropropylene, which is used clinically for permanent surgical sutures and thus proven to be biocompatible.9 In addition, fluorinated copolymer coating has been shown in ex vivo studies to be thromboresistant compared with CoCr BMS (Multi-Link Vision).21

Complex lesion characteristics and underlying unstable plaque morphologies are associated with greater delayed healing after first-generation DES placement compared with simple and stable coronary artery disease lesions.3,4 The present study demonstrated greater strut coverage in CoCr-EES versus SES and PES regardless of lesion characteristics, which is in agreement with several registry-based studies and a pooled analysis from randomized clinical trials showing the safety and efficacy of CoCr-EES versus first-generation DES in patients with acute coronary syndromes, long or small-vessel lesions, and unprotected left main coronary disease.22–25 A recent randomized comparison of CoCr-EES and BMS in patients with ST-segment elevation acute myocardial infarction showed a significantly lower incidence of TLR and stent thrombosis in CoCr-EES versus BMS at 1 year after stent implantation.26

Figure 6. Neoatherosclerosis in cobalt-chromium everolimus-eluting stents (CoCr-EES). A, Histological sections from a 49-year-old man with CoCr-EES implanted in the mid left anterior descending coronary artery 2 years antemortem. A low-power image (a) (Movat) shows a patent lumen with moderate neointimal growth (50% cross-sectional area narrowing). b, A high-power image of the boxed area in a shows foamy macrophage accumulation within the neointima close to the luminal surface, which is confirmed by immunostaining for CD68-positive macrophages (c). B, Histological sections from a 73-year-old man with CoCr-EES implanted in the mid left anterior descending coronary artery for 3 years. A low-power image (d) (Movat) shows moderate luminal narrowing with moderate neointimal growth (69% stenosis) and underlying fibroatheroma. NC indicates necrotic core. A high-power image (e) of the boxed area in d shows necrotic core formation within the neointima where CD68-positive macrophages are identified (f). *Stent strut.
Although a long-term follow-up for safety and efficacy of CoCr-EES in these settings is still needed, our pathological findings support greater clinical safety of CoCr-EES versus first-generation DES for off-label indications.

Hypersensitivity vasculitis with eosinophils and T lymphocytes has been shown to be an important pathological etiology of LST/VLST in SES, which is likely a response to the polymer rather than the drug. Reduced inflammation without hypersensitivity vasculitis in CoCr-EES could be attributed to greater biocompatibility of the fluorinated copolymer, although the limited sample size in the present study must be taken into consideration. In a porcine coronary model, CoCr-EES showed similar or even greater inflammation compared with SES at 28 and 90 days after stent placement; however, decreasing inflammatory response was observed in CoCr-EES over time, whereas SES showed an escalating amount of inflammation up to 1 year. On the other hand, malapposition with excessive fibrin deposition is known to be associated with PES thrombosis. When it is considered that the cytotoxic drug paclitaxel showed a dose-dependent increase in fibrin deposition in preclinical animal models, reduced fibrin deposition in CoCr-EES might be partly attributable to an optimal dose of the cytostatic drug everolimus and its better release kinetics. Clinical imaging studies have demonstrated that VLST after first-generation DES placement is associated with late acquired malapposition and positive vessel remodeling. In the present study, reduced inflammation and less fibrin deposition in CoCr-EES was accompanied by a lower frequency of malapposition, which may contribute to the decrease in LST/VLST.

CoCr-EES failed to show a reduction in the prevalence of neoatherosclerosis versus SES and PES in this study population, although the morphology of neoatherosclerosis in CoCr-EES was characterized mostly by foamy macrophage infiltration in comparison to SES. It has been reported that first-generation DES develop neoatherosclerosis rapidly and more frequently compared with BMS; no neoatherosclerosis was identified in BMS implanted for ≤2 years. It is believed that accelerated neoatherosclerosis in first-generation DES might be secondary to incompetent regenerated endothelium with poor cell-to-cell junctions that characterize impaired endothelial barrier function. In rabbit iliac arteries, CoCr-EES showed greater expression of platelet endothelial cell adhesion molecule-1, a transmembrane protein, versus SES and PES at 14 days after stent implantation. However, all DES showed decreased expressions of platelet endothelial cell adhesion molecule-1, a transmembrane protein, versus SES and PES at 14 days after stent implantation. However, all DES showed decreased expressions of platelet endothelial cell adhesion molecule-1, a transmembrane protein, versus SES and PES at 14 days after stent implantation. However, all DES showed decreased expressions of platelet endothelial cell adhesion molecule-1, a transmembrane protein, versus SES and PES at 14 days after stent implantation.
cell adhesion molecule-1 and antithrombotic cofactor thrombomodulin compared with BMS, which may at least partly indicate that endothelial maturation is still insufficient in CoCr-EES compared with BMS.\textsuperscript{30}

Differential stent design, distortion, or acquired underexpansion, along with straightening of the artery and motion, enhances the possibility of fracture. The incidence of CoCr-EES fracture as clinically assessed by fluoroscopy or intravascular ultrasound has been reported recently to be 2.9%; lesions with fracture versus those without fracture showed significantly greater prevalence of TLR (25.6% versus 2.0%) and stent thrombosis (5.1% versus 0.4%) at 9 months after stent placement.\textsuperscript{31} The higher observed frequency of CoCr-EES fracture in our autopsy lesions (13%) versus the clinical study could be explained in part by the superior resolution of the high-contrast film–based radiography (80 μm) versus fluoroscopy (300 μm) or intravascular ultrasound (200 μm) or may represent the very selected sample enriched with increased stent-related adverse events in the present study. Our radiographic analysis demonstrated that the majority of CoCr-EES fractures occur in the nonlinear link, which is intended to provide greater flexibility and conformability to the stents but at the same time could be a nidus for fatigue fracture, which may induce thrombosis or restenosis. Stent design, type of metal, and conformability of the stent to the artery curvature all contribute to stent fracture, and therefore a more sensitive assessment may be needed by designing a more strenuous and clinically relevant method such as bending fatigue testing rather than radial pulsatile fatigue testing, which is required by the Food and Drug Administration.

When it is considered that neoatherosclerosis develops and progresses over time, similarly, the frequency of stent fracture increases with advancing duration of implantation probably because of continuous stress on the stents and metal fatigue\textsuperscript{5,6}; the contribution of these factors to vascular complications is required at a later time. Progressive increases in neointimal thickness together with a substantial prevalence of neoatherosclerosis and fracture-related restenosis in CoCr-EES observed in the present study indicate that careful long-term follow-up is still required even after CoCr-EES placement, and further improvements in stent technologies are needed to overcome these issues.

\textbf{Study Limitations}

There is an inherent bias in studies involving an autopsy population with a relatively greater number of patients dying from DES complications compared with clinical studies that have a defined large population of living patients. Nevertheless, clinical studies lack information on the precise nature of the complication because resolution of imaging modalities is limited and the nature of the defect at the time of death usually cannot be studied and can only be surmised from history. Our study population consisted of subjects with consecutive lesions with DES from the all-comer autopsy registry in which the duration of implantation could not be matched completely, although the dependence of vascular responses on duration of implantation was corrected with multiple regression analyses. In the present study, detailed clinical information, including risk factors and dual antiplatelet therapy, was available only in a limited number of cases. Although greater stent healing

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\textsuperscript{ACS indicates acute coronary syndromes; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; Ex, Express; FS, fracture site; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LM, left main coronary artery; LOM, left obtuse marginal branch; LST, late stent thrombosis; ML, Multi-Link; NCD, noncardiac death; NSRCD, non-stent-related cardiac death; RCA, right coronary artery; SRD, stent-related death; and SVG, saphenous vein graft.}

\textsuperscript{*Data derived from previously published case (Foerst JR, Ball TC, Nakano M, Virmani R, Kaplan AV. Late complication: Xience V stent fractures with restenosis. \textit{JACC Cardiovasc Interv} 2012;5:239–243).
in CoCr-EES versus first-generation DES was observed consistently across different lesion characteristics and durations of implantation, the manner in which these findings can be extrapolated to living patients is difficult to ascertain but may be linked. The present study did not show direct evidence for linking the development of neatherosclerosis with late vascular complications in CoCr-EES because the duration of implantation was relatively short (median = 200 days). A substantial number of the autopsy cases came from noncardiac or non-stent-related cardiac deaths, and the relationship of the pathological findings observed in those lesions to clinical events cannot be determined.

Conclusions
CoCr-EES compared with SES and PES showed less LST/VLST with fewer uncovered struts, less inflammation (with no hypersensitivity reaction), and less fibrin deposition in humans; greater strut coverage of CoCr-EES was consistently observed irrespective of lesion characteristics and indications for stenting. Our results support greater clinical safety of CoCr-EES compared with first-generation DES; the importance of long-term clinical follow-up should also be emphasized with appropriate tools to investigate outcomes because progressive neointimal growth with similar frequency of neatherosclerosis and fracture-related adverse events was observed even after CoCr-EES placement.

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References

**CLINICAL PERSPECTIVE**

Clinical trials have demonstrated that the second-generation cobalt-chromium everolimus-eluting stent (CoCr-EES) is superior to the first-generation paclitaxel-eluting stent and is noninferior or superior to the sirolimus-eluting stent in terms of safety and efficacy. However, histological vascular responses to the CoCr-EES versus the sirolimus-eluting stent and paclitaxel-eluting stent have not been reported in humans. The present autopsy study demonstrated for the first time that CoCr-EES exhibit significantly greater strut coverage with less inflammation (with no case of hypersensitivity) and fibrin deposition and a decrease in late stent thrombosis compared with first-generation drug-eluting stents in humans. In addition, greater strut coverage in CoCr-EES versus sirolimus-eluting stents and paclitaxel-eluting stents was observed consistently irrespective of lesion characteristics and indications for stenting. These findings support greater clinical safety of CoCr-EES versus first-generation drug-eluting stents, even for “off-label” indications. On the other hand, the present study also revealed that CoCr-EES showed progressive neointimal growth up to 3 years, which was similar to first-generation drug-eluting stents. Moreover, the prevalence of neoatherosclerosis and fracture-related adverse events (restenosis or thrombosis) in CoCr-EES was comparable to that in sirolimus-eluting and paclitaxel-eluting stents. It is believed that neoatherosclerosis develops and progresses over time, and, similarly, the frequency of stent fracture increases with advancing duration of implantation because of continuous stress on the stents and metal fatigue. The present pathological findings indicate that careful long-term follow-up is still required even after CoCr-EES placement.
Pathology of Second-Generation Everolimus-Eluting Stents Versus First-Generation Sirolimus- and Paclitaxel-Eluting Stents in Humans

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