ORIGINAL RESEARCH

Very Late Pathological Responses to Cobalt–Chromium Everolimus-Eluting, Stainless Steel Sirolimus-Eluting, and Cobalt–Chromium Bare Metal Stents in Humans

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***Background*—**The "very late" clinical outcomes for durable polymer drug-eluting stents and bare metal stents (BMSs) have been shown to be dissimilar in clinical studies. Conceptually, the long-term vascular compatibility of BMSs is still regarded to be superior to drug-eluting stents; however, no pathologic study to date has specifically addressed this issue. We evaluated the very late (≥1 year) pathologic responses to durable polymer drug-eluting stents (cobalt–chromium [CoCr] everolimus-eluting stents [EESs] and stainless steel sirolimus-eluting stents [SS-SESs]) versus BMSs (CoCr-BMSs).

***Methods and Results*—**From the CVPath stent registry, we studied a total of 119 lesions (40 CoCr-EESs, 44 SS-SESs, 35 CoCr-BMSs) from 92 autopsy cases with a duration ranging from 1 to 5 years. Sections of stented coronary segments were pathologically analyzed. Inflammation score and the percentage of struts with giant cells were lowest in CoCr-EESs (median inflammation score: 0.6; median percentage of struts with giant cells: 3.8%) followed by CoCr-BMSs (median inflammation score: 1.3 [$P<0.01$]; median percentage of struts with giant cells: 8.9% [$P=0.02$]) and SS-SESs (median inflammation score: 1.7 [$P<0.01$]; median percentage of struts with giant cells: 15.3% [$P<0.01$]). Polymer delamination was observed exclusively in SS-SESs and was associated with increased inflammatory and giant cell reactions. The prevalence of neoatherosclerosis with CoCr-EESs (50%) was significantly less than with SS-SESs (77%, $P=0.02$) but significantly greater than with CoCr-BMSs (20%, $P<0.01$).

***Conclusions*—**CoCr-EESs, SS-SESs, and BMSs each demonstrated distinct vascular responses. CoCr-EESs demonstrated the least inflammation, near-equivalent healing to BMSs, and lower neointimal formation. These results challenge the belief that BMSs have superior biocompatibility compared with some polymeric coated drug-eluting stents and may have implications for future stent design. **(*J Am Heart Assoc*. 2017;6:e007244. DOI: 10.1161/JAHA.117.007244.)**

Key Words: bare metal stent • drug-eluting stent • inflammation • neoatherosclerosis • pathology

Percutaneous coronary intervention using durable polymer (DP) drug-eluting stents (DESs) has been the most common strategy to treat patients with symptomatic coronary artery disease.[1] Use of first-generation DESs reduced in-stent restenosis rates compared with bare metal stents (BMSs); however, their use was associated with late and "very late" stent thrombosis[2] due to delayed arterial healing characterized by uncovered struts.[3] Inflammatory responses and hypersensitivity reactions were also greater with first-generation DESs versus BMSs.[3] Second-generation DESs introduced in 2005 had thinner stent struts, more biocompatible DPs, and marginally lower drug doses, resulting in reduced early and late stent thrombosis rates.[4] A human pathological study confirmed better healing with less inflammation in contemporary cobalt–chromium (CoCr) everolimus-eluting stents (EESs) versus first-generation DESs, although most of the stents examined were implanted for <1 year.[5]

Newer generation DESs have been made with biodegradable polymer (BP) or polymer-free technology on the assumption that DPs are potentially harmful and that BMS surfaces have more favorable long-term outcomes. However, the very late (≥1-year) pathological responses in humans comparing DP-DES and BMS surfaces have never been studied.

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/6/11/e007244/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- The biocompatibility of bare metal stents has been assumed to be superior to that of durable polymer–based drug-eluting stents.
- In this pathology study of human bare metal stent, second-generation cobalt–chromium everolimus-eluting stent, and first-generation stainless steel sirolimus-eluting stent implants with a duration ranging from 1 to 5 years, cobalt–chromium everolimus-eluting stents showed the least inflammatory reaction, followed by bare metal and stainless steel sirolimus-eluting stents, respectively.

What Are the Clinical Implications?

- These results raise questions about the belief that biocompatibility is best with bare metal surfaces and suggest that the fluoropolymer coating of cobalt–chromium everolimus-eluting stents may have more favorable vascular responses.

We aimed to understand the long-term pathological results of CoCr-EESs compared with similarly designed CoCr-BMSs and stainless steel sirolimus-eluting stents (SS-SES) using our registry of human DES implants.

Methods

Patients and Lesions

Between 2005 and 2015, the CVPath stent registry had received a total of 990 lesions from 582 cases. From this registry, after exclusion of stent lesions in bypass grafts, we collected all CoCr-EESs (XIENCE; Abbott Vascular) and CoCr-BMSs (MULTI-LINK VISION; Abbott Vascular) with a duration of implantation ranging from 1 to 5 years in our registry. This study was approved by an institutional review board at CVPath institute. Because this was autopsy study, the requirement for informed consent was waived. A total of 40 CoCr-EES lesions and 35 CoCr-BMS lesions were identified. Ten lesions from CoCr-EES and 2 lesions from SS-SES groups were used in a previous study and were also included in the present study.[5] Because SS-SESs (CYPHER; Cordis Corp) were discontinued at the end of 2011, all lesions (n=44) with duration of implantation from 1 to 5 years from 2008 to 2011 in the CVPath stent registry were selected as historical controls. Consequently, a total of 119 lesions from 92 cases with similar duration of implantation were evaluated in the present study. In hearts with multiple stents, overlapping and consecutively implanted stents were treated as 1 lesion, whereas stents showing gaps of >5 mm were considered separate lesions.[6] All available clinical records were reviewed for patient history, duration of implantation, and risk factors. Cause of death was determined to be stent-related, non–stent-related cardiac, or noncardiac death, as described previously.[6]

Histological Preparation

Following fixation with 10% neutral buffered formalin, epicardial coronary arteries were removed from the heart and radiographed and decalcified as necessary, and the entire stented segments were dehydrated and embedded in methyl methacrylate plastic. In brief, the plastic-embedded stents were segmented at 3-mm intervals, sectioned at 4 to 6 μm, and stained with hematoxylin and eosin and modified Movat pentachrome stains, as described previously.[7]

Pathological Assessment and Morphometric Analysis

Underlying plaque morphology was categorized as pathological intimal thickening, fibroatheroma, thin-cap fibroatheroma, and fibrocalcific plaque, according to modified American Heart Association classification.[8] Lesion calcification was categorized as none, mild, moderate, or severe, based on radiograph.[9] Stent fracture was assessed by x-ray and reported as prevalence of grade V fracture, which required complete separation of stent struts with a gap.[9] Morphometric

Table 1. Patient Characteristics

	CoCr-EES	SS-SES	CoCr-BMS	*P* Value
Patients, n	32	33	28	
Age, y, mean±SD	63±14	59±12	61±17	0.53
Male	25 (78)	20 (61)	20 (71)	0.30
Hypertension	21/25 (84)	18/24 (75)	15/20 (75)	0.68
Diabetes mellitus	7/25 (28)	10/24 (42)	9/20 (45)	0.45
Hyperlipidemia	10/25 (40)	8/24 (33)	9/20 (45)	0.73
Smoking	3/25 (12)	3/24 (13)	6/20 (30)	0.21
Renal failure	4/25 (16)	6/24 (25)	5/20 (25)	0.68
Dialysis	2/25 (8)	4/24 (17)	2/20 (10)	0.62
Previous MI	18 (56)	15 (45)	18 (64)	0.33
Previous CABG	7 (22)	4 (12)	2 (7)	0.24
Cause of death				0.34
SRD	4 (13)	8 (24)	9 (32)	
NSRCD	16 (50)	16 (48)	9 (32)	
NCD	12 (38)	9 (27)	10 (36)	

Data are shown as n (%) except as noted. CABG indicates coronary artery bypass grafting; CoCr-BMS, cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; MI, myocardial infarction; NCD, noncardiac death; NSRCD, non–stent-related cardiac death; SRD, stent-related death; SS-SES, stainless steel sirolimus-eluting stent.

Table 2. Lesion Characteristics

	Lesions			*P* Value	
	CoCr-EES (n=40)	SS-SES (n=44)	CoCr-BMS (n=35)	CoCr-EES vs SS-SES	CoCr-EES vs CoCr-BMS
Duration of implantation, y, median (IQR)	2.0 (1.5–3.0)	2.0 (1.0–3.1)	2.0 (1.5–3.2)	0.78	0.93
Indication for stenting				0.97	0.51
Stable CAD	28 (70)	31 (70)	27 (77)		
ACS	12 (30)	13 (30)	8 (23)		
Lesion location				0.18	0.23
LM	2 (5)	2 (5)	1 (3)		
LAD	20 (50)	17 (39)	12 (34)		
LCX	9 (23)	9 (20)	11 (31)		
RCA	9 (23)	16 (36)	11 (31)		
Stent length, mm, median (IQR)	21 (15–37)	22 (15–32)	20 (15–28)	0.52	0.36
No. of stents per lesion				0.50	0.18
1	23 (58)	29 (66)	26 (74)		
2	12 (30)	10 (23)	6 (17)		
≥3	5 (13)	5 (11)	3 (9)		
Overlapping stents	18 (45)	15 (34)	9 (26)	0.34	0.11
Bifurcation multistenting	3 (8)	3 (7)	2 (6)	0.92	0.70
Underlying plaque morphology				0.99	0.76
TCFA or rupture	9 (23)	13 (30)	5 (14)		
Fibroatheroma	4 (10)	6 (14)	3 (9)		
Fibrocalcific plaque	20 (50)	19 (43)	15 (43)		
PIT	7 (18)	6 (14)	12 (34)		
Lesion calcification				0.82	0.89
None	2 (5)	6 (14)	6 (17)		
Mild	13 (33)	9 (20)	9 (26)		
Moderate	14 (35)	22 (50)	16 (46)		
Severe	11 (28)	7 (16)	4 (11)		
Prevalence of grade V fracture	2 (5)	10 (23)	1 (3)	0.03	0.62
Pathological stent failure*	4 (10)	13 (30)	18 (51)	0.03	<0.01
Restenosis	1 (3)	4 (9)	10 (29)	0.22	<0.01
Thrombosis (very late)	2 (5)	7 (16)	3 (9)	0.12	0.54
CTO	2 (5)	3 (7)	7 (20)	0.72	0.06

Data are shown as n (%) except as noted. Generalized estimating equation model with ordinal logistic model was used for statistical analysis as described in the methods. Grade V fracture required complete separation of stent struts with a gap. ACS indicates acute coronary syndrome; CAD, coronary artery disease; CoCr-BMS, cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; CTO, chronic total occlusion; IQR, interquartile range; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; PIT, pathological intimal thickening; RCA, right coronary artery; SS-SES, stainless steel sirolimus-eluting stent; TCFA, thin cap fibroatheroma.
*Some thrombosis lesions came with restenosis or CTO.

measurements were performed with image analysis software (Zen2, blue edition; Carl Zeiss) after digital scanning and included external elastic lamina, internal elastic lamina, stent area, lumen area, underlying plaque area, and neointimal area as well as the neointimal thickness above each strut. Stent thrombosis was defined as a platelet-rich thrombi occupying >30% of the cross-sectional area and was regarded as very late stent thrombosis (VLST) because of the duration (≥1 year).[10] In-stent restenosis was defined as >75% cross-sectional luminal area narrowing by neointimal tissue within stent area, with or without atheroslcerosis.[11] In-stent chronic total occlusion was defined as being when stent lumen was

Table 3. Pathologic Assessment

	Lesions			*P* Value	
	CoCr-EES (n=40)	SS-SES (n=44)	CoCr-BMS (n=35)	CoCr-EES vs SS-SES	CoCr-EES vs CoCr-BMS
Histological sections evaluated, n	265	298	229		
Stent struts evaluated, n	3165	2941	2749		
External elastic lamina area, mm^2	13.0 (11.7–15.6)	14.3 (9.7–17.9)	12.8 (9.5–14.9)	0.46	0.53
Internal elastic lamina area, mm^2	11.9 (10.6–14.1)	13.1 (8.5–16.2)	11.7 (8.5–13.4)	0.52	0.48
Stent area, mm^2	7.2 (5.2–8.1)	7.5 (5.6–9.4)	6.1 (5.0–7.8)	0.28	0.74
Underlying plaque area, mm^2	5.1 (3.3–6.0)	4.5 (2.7–7.3)	3.9 (2.4–6.3)	0.92	0.49
Mean neointimal area, mm^2	1.2 (0.9–1.7)	1.2 (0.7–1.8)	1.9 (1.7–2.7)	0.47	<0.01
Mean neointimal thickness, mm	0.18 (0.12–0.29)	0.17 (0.11–0.25)	0.37 (0.28–0.50)	0.91	<0.01
Maximum neointimal thickness, mm	0.33 (0.22–0.49)	0.34 (0.23–0.54)	0.58 (0.44–0.73)	0.70	<0.01
Mean percentage of uncovered struts per lesion, %	0 (0–2.4)	2.5 (0–7.4)	0 (0–0)	0.05	<0.01
Rate of lesion with >30% uncovered struts in ≥1 cross-section*	3 (8%)	12 (27%)	0 (0%)	<0.01 (overall)	
Mean percentage of strut with fibrin per lesion, %	0.3 (0–6.3)	5.4 (0–14.0)	0.8 (0–4.4)	0.05	0.69
Maximum no. of eosinophils per strut†	0 (0–0.3)	0.7 (0–4.6)	0.3 (0–0.8)	<0.01	0.29
Rate of hypersensitivity reaction*	0 (0%)	7 (16%)	1 (3%)	<0.01 (overall)	
Neovascularization score	0.5 (0.2–1.7)	0.9 (0–2.1)	2 (1.0–3.2)	0.42	<0.01

Data are shown as median (interquartile range) except as noted. GEE method with γ with log-link model was used unless specified. CoCr-BMS indicates cobalt-chromium bare metal stent; CoCr-EES, cobalt-chromium everolimus-eluting stent; GEE, generalized estimating equation; SS-SES, stainless steel sirolimus-eluting stent.

*Tabular Fisher exact test was substituted because GEE fails as a result of low observed frequency.

†GEE with Poisson loglinear model was selected.

occupied with organizing or organized thrombus, as described previously.[12] Pathological stent failure at autopsy was defined as a composite of restenosis, stent thrombosis, or chronic total occlusion.

Uncovered struts were reported as the ratio of uncovered to total struts per section.[6] Strut coverage was also assessed on the basis of the presence or absence of >30% uncovered struts in at least 1 cross-section.[6] The degree of fibrin deposition was reported as the percentage of struts with fibrin.

The severity of inflammation was evaluated 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: ≥2 strut-associated granulomatous inflammatory reactions).[5] The percentage of stent struts with giant cells and the maximum number of eosinophils per strut were also evaluated. Hypersensitivity reaction was determined as diffuse circumferential inflammation predominantly consisting of T lymphocytes and eosinophils. Neovascularization associated with stent struts was evaluated on the basis of a grading scale of 0 to 4 (score 0: absent; score 1: <25% struts with ≥2 microvessels; score 2: 25–50% struts with ≥2 microvessels; score 3: 51–75% struts with ≥2 microvessels; score 4: >75% struts with ≥2 microvessels).

Polymer delamination was defined when there was isolated polymer remote from stent struts in DESs, and it was reported at the lesion level. Neoatherosclerosis (newly formed atherosclerotic change within the stented segment) was categorized as foamy macrophage, fibroatheroma, thin-cap fibroatheroma, and in-stent plaque rupture.

Statistical Analyses

Normality of data was tested with the Shapiro–Wilk test. Continuous variables with normal distribution were expressed as mean±SD and continuous variables with nonnormal distribution were expressed as median value (25th–75th percentile). Categorical variables were expressed as number (percentage). For patient-level analysis, comparisons of continuous variables with normal distribution were tested by 1-way ANOVA, and categorical variables were analyzed by Fisher exact or χ^2 test. For lesion-level analysis, the generalized estimating equation (GEE) method was used. Continuous variables were tested by the GEE method with γ

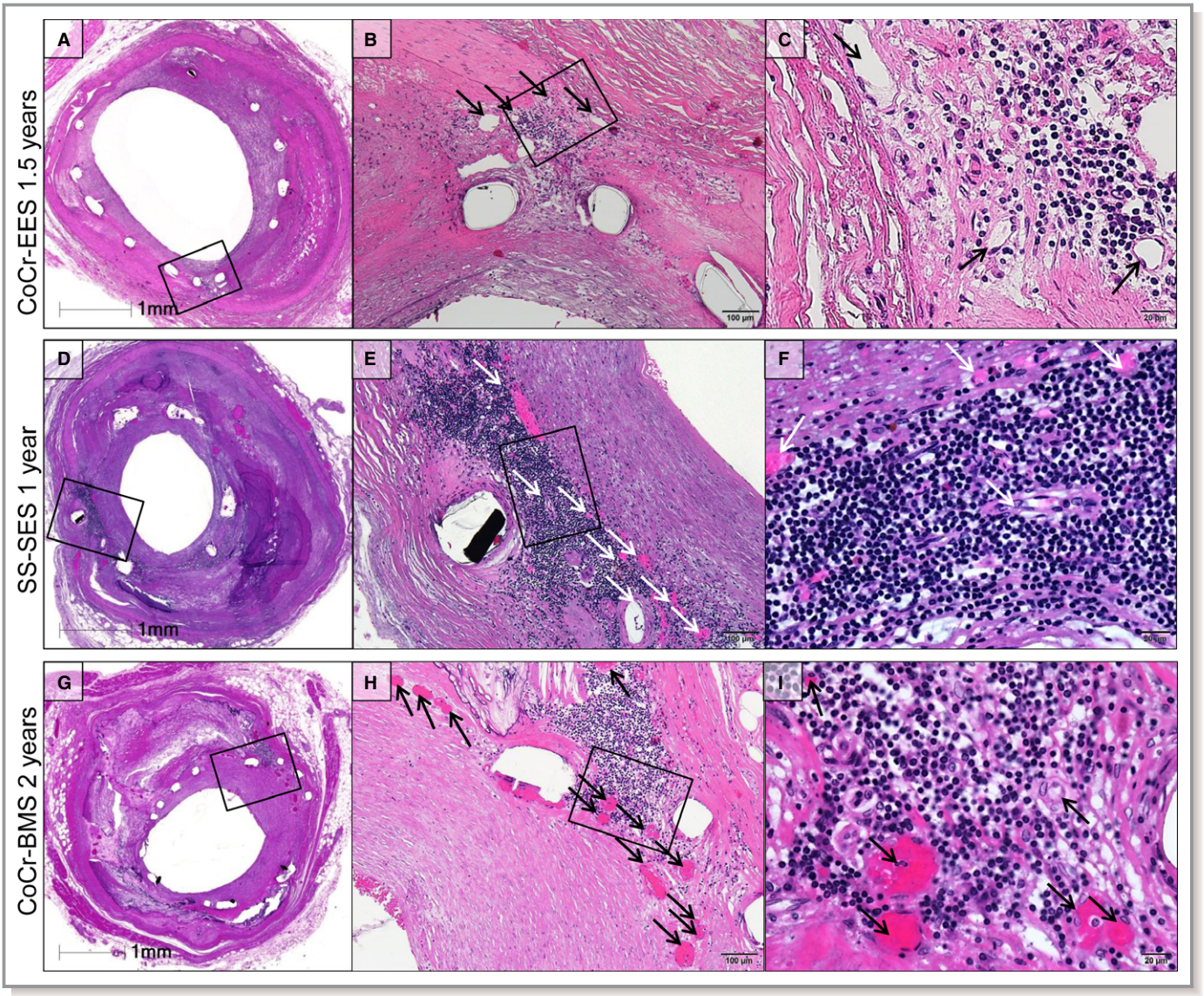


Figure 1. Representative images of stent-associated local inflammation. A through C, A CoCr-EES lesion in the mid–left anterior descending artery of 1.5-year duration from a 54-year-old man who died of head injury. The low-power image in (A) shows the CoCr-EES implanted over fibrocalcific plaque. The middle-power image in (B) shows minimal neovascularization (black arrows), whereas the high-power image in (C) shows mild inflammatory reaction. D through F, An SS-SES lesion in the proximal left circumflex artery of 1-year duration from a 70-year-old man with a history of hemodialysis who died of a noncardiac cause following a syncopal episode. The low-power image in (D) shows the SS-SES implanted over a fibrocalcific plaque. The middle-power image in (E) shows moderate neovascularization (white arrows), whereas the high-power image in (F) shows a severe inflammatory reaction localized around the stent struts. G through I, A CoCr-BMS lesion in the mid–left circumflex artery of 2 years duration from a 63-year-old man who died of pulmonary fibrosis. The low-power image in (G) shows the CoCr-BMS implanted over fibrocalcific plaque. The middle-power image in (H) shows numerous areas of neovascularization (black arrows), whereas the high-power image in (I) shows a moderate inflammatory reaction. All images were stained with hematoxylin and eosin. CoCr-BMS indicates cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; SS-SES, stainless steel sirolimus-eluting stent.

with the log-link or Poisson model, as appropriate. Categorical data were tested by the GEE method with an ordinal logistic model or tubular Fisher exact test, as appropriate. Subgroup analysis for very late vascular responses (inflammation and neoatherosclerosis) used the GEE method with a binary logistic model. All GEE analyses were performed with hierarchic adjustment (lesions nested within patients). These comparisons were adjusted for multiple comparisons, and CoCr-EESs served as the control. Working correlations used for GEE analyses were independent, AR(1), exchangeable and M-dependent, and unstructured. JMP 9 (SAS Institute) or SPSS software version 22 (IBM Corp) were used for statistical analysis. P values <0.05 were considered statistically significant.

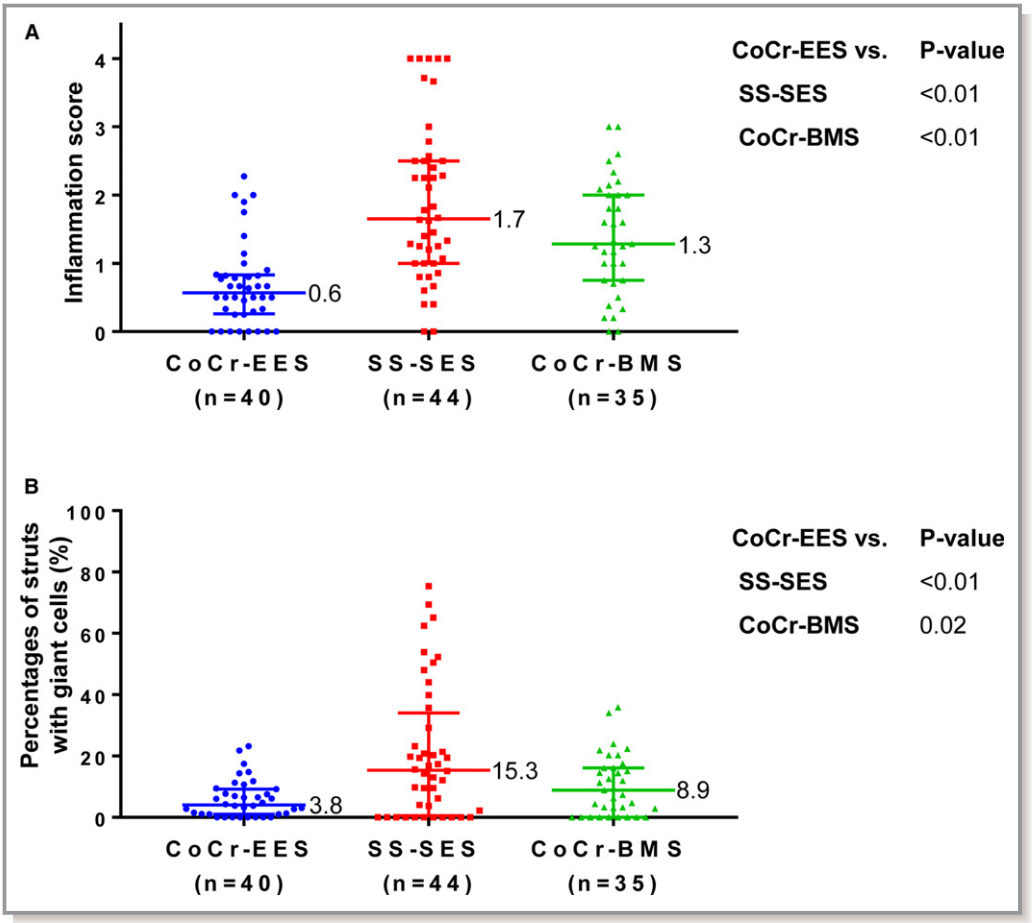


Figure 2. Extent of inflammation by stent type. Graphs show inflammation score (A) and percentage of struts with giant cells (B). Bars indicate median value with interquartile range. CoCr-BMS indicates cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; SS-SES, stainless steel sirolimus-eluting stent.

Results

Patient and Lesion Characteristics and Outcomes

Table 1 shows patient characteristics. There were no differences in clinical characteristics including age, sex, and cause of death with CoCr-EESs, SS-SESs, or CoCr-BMSs. Patient risk factors were also similar. Table 2 shows lesion characteristics and stent outcomes. Duration of stent implantation was similar. There were no differences in indication for stenting, lesion location, stent length, number of stents per lesion, bifurcation multistenting, underlying plaque morphology, and lesion calcification between groups.

Prevalence of grade V stent fracture was greatest in SS-SESs followed by CoCr-EESs and CoCr-BMSs (23%, 5%, and 3%, respectively). Pathological stent failure at autopsy was lowest in CoCr-EESs, followed by SS-SESs and CoCr-BMSs (10%, 30%, and 51%, respectively), with a significant difference between CoCr-EESs and CoCr-BMSs ($P<0.01$). The prevalence of restenosis and chronic total occlusion was greatest in CoCr-BMSs, whereas stent thrombosis (VLST) was highest with SS-SESs (Table 2).

Pathological Analysis and Morphometric Analysis

Table 3 shows morphometric and pathological analyses. No differences were observed in the external elastic lamina area, internal elastic lamina area, stent area, and underlying plaque area. CoCr-BMSs showed the greatest mean neointimal area, mean neointimal thickness, and maximum neointimal thickness, whereas these were comparable for CoCr-EESs and SS-SESs. Percentage of uncovered struts was lowest in CoCr-BMSs, followed by CoCr-EESs and SS-SESs. A considerable proportion of SS-SES–stented lesions had at least 1 cross-section with >30% uncovered struts, whereas this was much less frequently observed with CoCr-EESs and was not observed with CoCr-BMSs (27%, 7.5%, and 0%, respectively; $P<0.01$). SS-SESs showed greater fibrin deposition. No malapposed struts were observed in any groups.

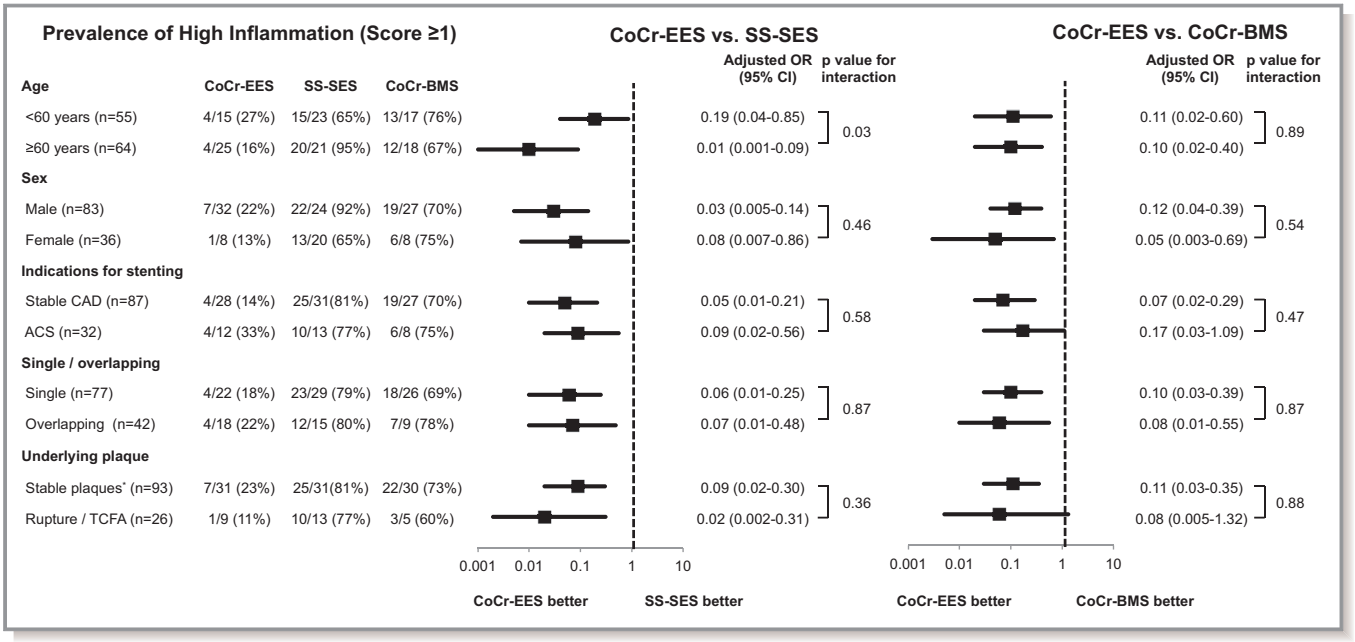


Figure 3. Subgroup analysis for the presence of high inflammation (score ≥1, A) and any neoatherosclerosis (B) with CoCr-EESs vs SS-SESs and CoCr-BMSs. Stable CAD includes fibroatheroma, fibrocalcific plaque, and pathological intimal thickening. ACS indicates acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; CoCr-BMS indicates cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; OR, odds ratio; SS-SES, stainless steel sirolimus-eluting stent; TCFA, thin-cap fibroatheroma.

Representative histological images are shown in Figure 1, and quantified data for inflammation and giant cell reaction are shown in Figure 2. Inflammation score was the lowest with CoCr-EESs (0.6; interquartile range [IQR]: 0.3–0.8), followed by CoCr-BMSs (1.3 [IQR: 0.8–2.0]; $P<0.01$), and highest with SS-SESs (1.7 [IQR: 1.0–2.5]; $P<0.01$). This trend remained even after exclusion of cases with target lesion failure (Table S1). Subgroup analyses are shown in Figure 3, in which the *P* value for interaction was not statistically different except for age. Similarly, the percentage of struts with giant cells was lowest with CoCr-EESs (3.8% [IQR: 0.3–8.8%]), followed by CoCr-BMSs (8.9% [IQR: 0–16.1%]; $P<0.01$), and highest with SS-SESs (15.3% [IQR: 0.6–34.6%]; $P=0.02$). SS-SESs showed significantly greater eosinophil infiltration than CoCr-EESs. Hypersensitivity reactions in DESs were observed exclusively in SS-SESs (16%) and were not observed in CoCr-EESs (0%), and reactions were present in only 1 CoCr-BMS case (3%). Neovascularization score was the highest with CoCr-BMSs (2 [IQR: 1.0–3.2]; $P<0.01$), followed by SS-SESs (0.9 [IQR: 0–2.1]; $P=0.42$) and CoCr-EESs (0.5 [IQR: 0.2–1.7]). SS-SESs showed significantly greater eosinophil infiltration than CoCr-EESs.

Figure 4A through 4D shows representative images of polymers and bar graphs showing prevalence of polymer delamination. The prevalence of polymer delamination in SS-SESs was 39% (17 of 44 lesions) at the lesion level, whereas its prevalence in CoCr-EESs was only 5% (2 of 40 lesions; $P<0.01$). In SS-SESs, lesions with polymer delamination showed higher inflammation scores than the lesions without polymer delamination (2.3 [IQR: 1.6–2.9] versus 1.3 [IQR: 0.8–2.4], respectively; $P=0.09$). Similarly, the percentage of struts with giant cells in SS-SESs was significantly higher in the lesions with polymer delamination than in lesions without polymer delamination (23.2% [IQR: 17.1–51.4%] versus 6.2% [IQR: 0–19.4%], respectively; $P=0.02$). In the 2 CoCr-EES lesions with polymer delamination, the lesion shown in Figure 4B had the highest inflammation score (2.3) of any CoCr-EES examined.

Representative images of neoatherosclerosis from each stent type are shown in Figure 5, and the prevalence and the type of neoatherosclerosis are shown in Figure 6. Prevalence of neoatherosclerosis with CoCr-EESs (50%) was significantly less than with SS-SESs (77%; $P=0.02$) but significantly more than with CoCr-BMSs (20%; $P<0.01$). Foamy macrophages and fibroatheroma were least prevalent with BMSs, whereas the least in-stent thin-cap fibroatheroma and rupture were present with CoCr-EESs. Subgroup analyses are shown in Figure 7, in which *P* values for interaction were not statistically different.

VLST was observed in 2 lesions with CoCr-EESs, 7 lesions with SS-SESs, and 3 lesions with CoCr-BMSs (Table 4). The 2 causes of VLST observed with CoCr-EESs were from uncovered struts in one case and from embolization from a prosthetic valve thrombus following transcatheter aortic valve replacement in the other. Seven lesions with SS-SESs showed varying causes of VLST (3 uncovered struts with or without hypersensitivity reactions, 2 in-stent plaque ruptures from

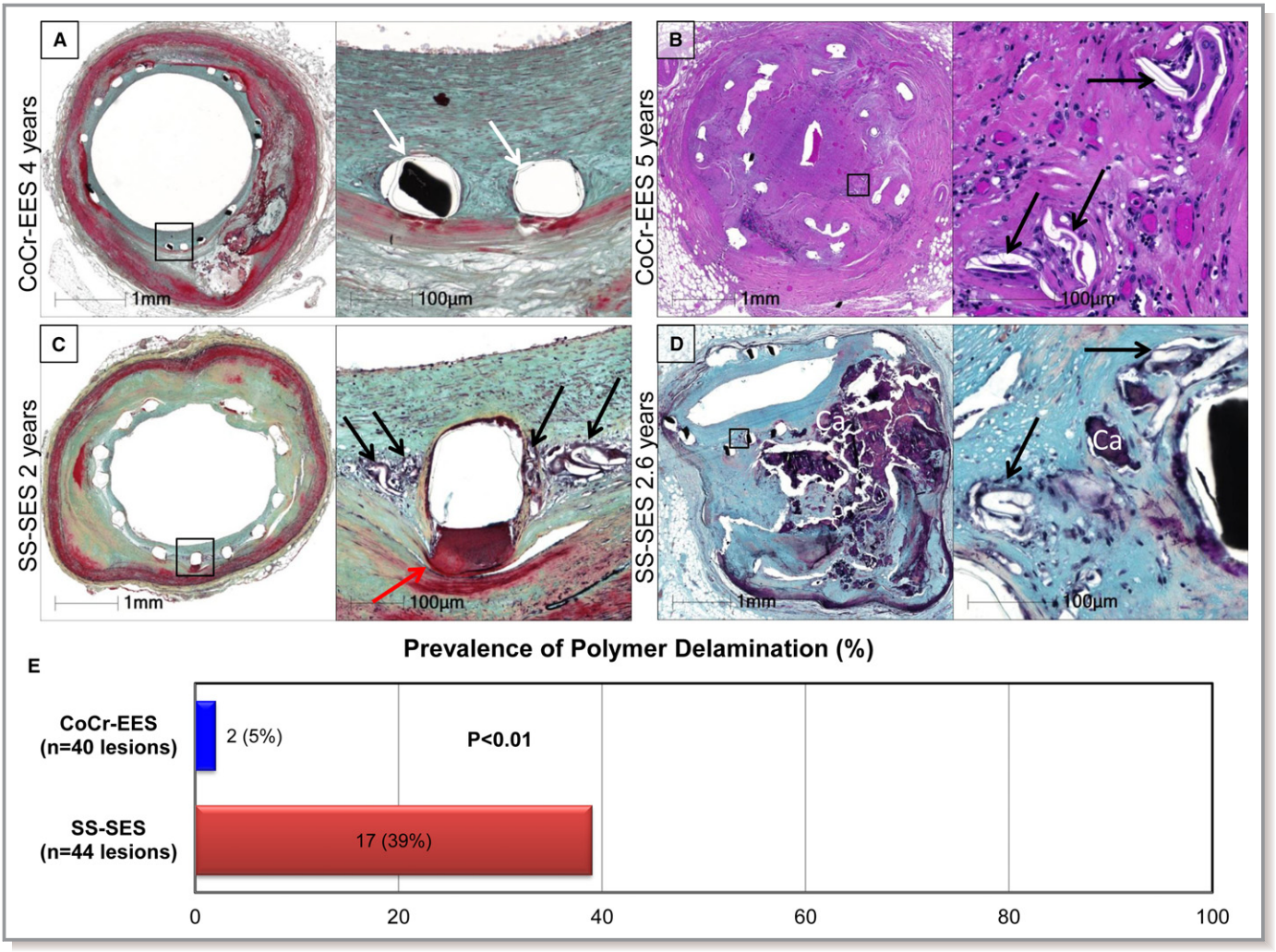


Figure 4. Polymer delamination. A, A CoCr-EES lesion in the mid–left anterior descending artery of 4-year duration from a 68-year-old man who was found unresponsive and died of noncardiac causes. The low-power image in (A) shows the CoCr-EES implanted over fibrocalcific plaque. The high-power image shows intact polymer (white arrows). B, A CoCr-EES lesion in the mid–left anterior descending artery of 5-year duration from a 59-year-old man who died of heart failure. The low-power image shows in-stent chronic total occlusion with polymer delamination associated with giant cell reaction in the high-power image (black arrows). C, An SS-SES lesion in the distal right coronary artery of 2-year duration from a 72-year-old man who died of heart failure. The low-power image in (C) shows the SS-SES implanted over a pathological intimal-thickening lesion. The high-power image shows delaminated polymer (black arrows), which is surrounded by giant cells. Fibrin deposition (red arrow) was also observed. All images were stained with Movat pentachrome staining. D, An SS-SES lesion in the distal left main artery of 2.6-year duration from a 55-year-old woman who died of hyperkalemia. The low-power image in (D) shows the SS-SES implanted over irregular calcification. The high-power image in (D) shows delaminated polymer (black arrows), which is surrounded by giant cells. Images in (A, B, and D) were stained with Movat pentachrome staining, whereas the image in (C) was stained with hematoxylin and eosin. E, Bar graph shows the prevalence of polymer delamination in CoCr-EESs vs SS-SESs. CoCr-EES indicates cobalt–chromium everolimus-eluting stent; SS-SES, stainless steel sirolimus-eluting stent.

neoatherosclerosis, and 2 neointimal erosions). Causes of VLST from 3 CoCr-BMS lesions were all in-stent plaque ruptures from neoatherosclerosis.

Discussion

The DES continues to be the primary device used for the interventional treatment of symptomatic coronary artery disease. We examined the very late (1- to 5-year implant duration) pathological response to 2 DP-DESs (first-generation SS-SES and second-generation CoCr-EES) in comparison to BMSs (the end product of BP-DESs) to determine which had a more favorable vascular response. CoCr-EESs appeared to have the most favorable histological response in terms of restenosis prevention, healing, and inflammatory reaction. A considerable proportion of SS-SESs had at least 1 section with >30% uncovered struts, whereas this was much less frequent with CoCr-EESs and absent with CoCr-BMSs.

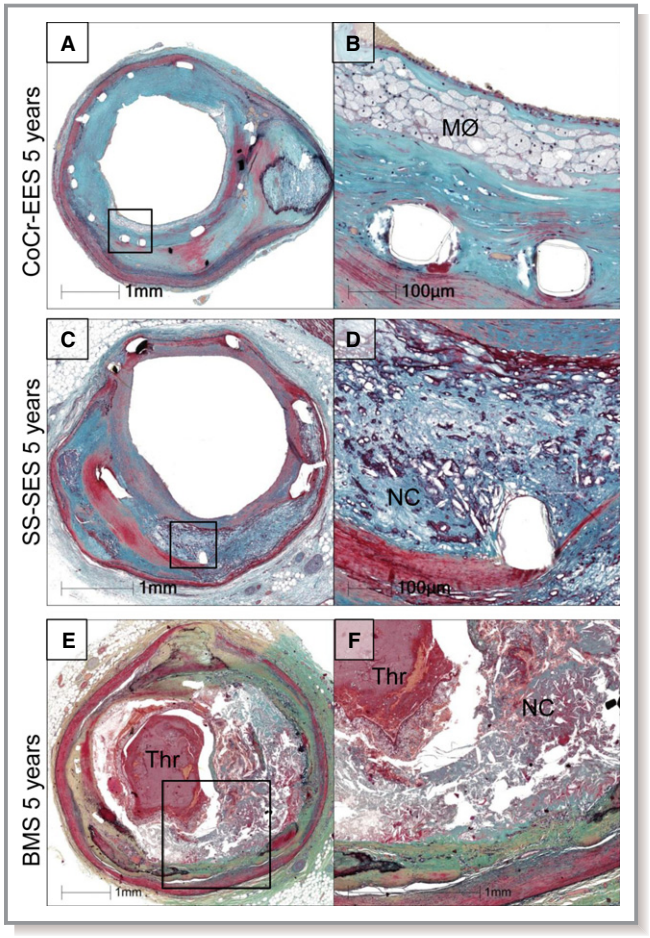


Figure 5. Neoatherosclerosis. A and B, A CoCr-EES lesion in the distal right coronary artery of 5-year duration from a 63-year-old man who died of diffuse severe coronary artery disease. The low-power image in (A) shows the CoCr-EES implanted over fibrocalcific plaque. The high-power image in (B) shows foamy macrophages (MØ) on the surface of neointima. C and D, An SS-SES lesion in the mid–left anterior descending artery of 5-year duration from a 40-year-old woman who died suddenly. The low-power image in (C) shows the SS-SES implanted over fibrocalcific plaque. The high-power image in (D) shows fibroatheroma with a calcified necrotic core (NC). E and F, A CoCr-BMS lesion in the distal right coronary artery of 5-year duration from a 56-year-old man who died of stent thrombosis. Both the low- and high-power images show plaque rupture from neoatherosclerosis accompanied by an occlusive thrombus (Thr). All images were stained with Movat pentachrome staining. BMS indicates bare metal stent; CoCr-BMS, cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; SS-SES, stainless steel sirolimus-eluting stent.

Inflammation and giant cell reaction were lowest with CoCr-EESs, followed by CoCr-BMSs, and highest in SS-SESs, with evidence of polymer delamination exclusively in the latter. The prevalence of neoatherosclerosis was significantly less with CoCr-EESs than with SS-SESs and significantly greater with either than with CoCr-BMS. Our results suggest that the response to each type of stent (even those within the same category) is highly specific and should not be generalized. Moreover, the responses to both CoCr-BMSs and CoCr-EESs were favorable, which suggests that each may have distinct advantages, as we discuss below.

Inflammatory Reaction

Long-term chronic inflammation has been linked to restenosis in both human pathologic specimens and animal models.[13] PEVA (poly[ethylene-co-vinyl acetate]) and PBMA (poly[*n*-butyl methacrylate]) were used on SS-SESs, whereas PVDF-HFP (poly[vinylidene fluoride-co-hexafluoropropylene]) is the polymer used in CoCr-EESs. The PVDF-HFP "fluoropolymer" used on CoCr-EESs adsorbs and retains albumin compared with BMSs, and this is thought to help minimize platelet adhesion and activation and leukocyte recruitment.[14] In a preclinical study, other fluoropolymer-coated metallic stents, in the absence of antiproliferative drugs, showed significantly less inflammation and less neointima than BMSs at 28 and 90 days in the coronary arteries of pigs.[15] In a porcine shunt model from the same study, thrombogenicity and inflammatory cell adherence were also less with fluoropolymer-coated stents than with BMSs.[15] In another study, CoCr-EESs showed the least thrombogenicity and cell adhesion compared with 4 types of current BP-DESs in the porcine shunt model.[16]

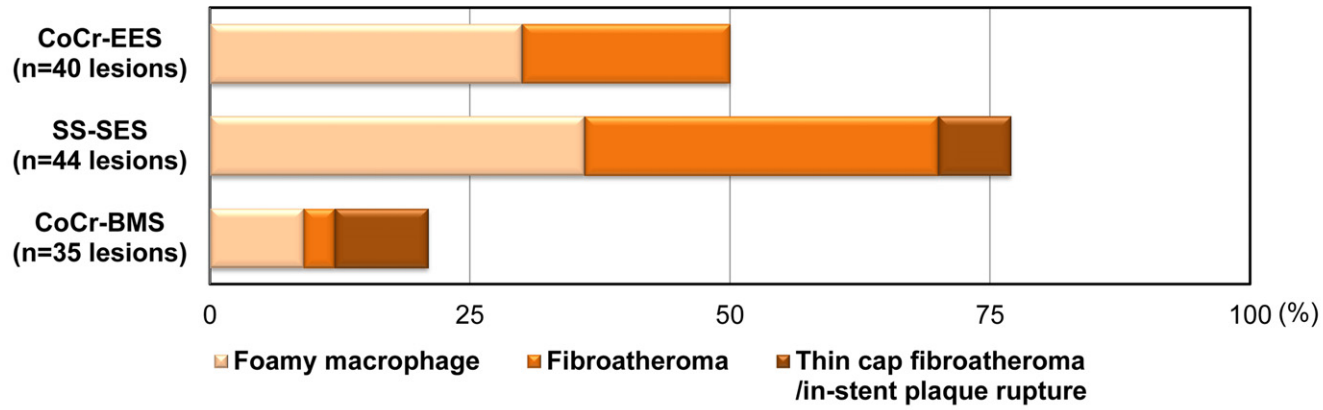
Metals themselves, such as those used in CoCr-EESs, can also provoke inflammation. The CoCr-BMS examined in this study consists of cobalt, chromium, tungsten, and nickel, of which the latter is thought to be the most immunogenic and a common cause of allergic contact dermatitis.[17] To date, clinical studies of patients with nickel or chromium allergy receiving coronary stents have not shown early or late poor outcomes after stenting.[18]

Our data show that inflammation score was highest in SS-SES samples, followed by the CoCr-BMS, and lowest in the CoCr-EES. The findings comparing SS-SESs with CoCr-EESs are consistent with previous pathological studies.[5] Our study reveals, for the first time, that CoCr-EESs show less inflammatory reaction than CoCr-BMSs, a trend that was also observed in an animal study.[19] Meta-analyses and some clinical trials have suggested lower rates of stent thrombosis and target lesion revascularization with CoCr-EESs versus BMSs or BP-DESs.[20–22] These data are consistent with our findings and suggest that the data regarding the anti-inflammatory properties of the fluoropolymer used in CoCr-EESs may be operative in vivo over a long-time, up to 5 years.

Neoatherosclerosis

The long-term vascular response to stenting involves important temporal changes in the composition of the neointima that may or may not involve the influx of foamy macrophages.

A



B Prevalence and Type of Neoatherosclerosis

	CoCr-EES (n=40 lesions)	SS-SES (n=44 lesions)	CoCr-BMS (n=35 lesions)	P-value for CoCr-EES vs. SS-SES	P-value for CoCr-EES vs. CoCr-BMS
Prevalence of neoatherosclerosis (any)	20 (50%)	34 (77%)	7 (20%)	0.02	<0.01
Foamy macrophage	12 (30%)	16 (36%)	3 (9%)	0.71	0.01
Fibroatheroma	8 (20%)	15 (34%)	1 (3%)	0.15	0.04
TCFA or in-stent plaque rupture*	0 (0%)	3 (7%)	3 (9%)	0.18 (overall)	

C Distribution of Neoatherosclerosis

	CoCr-EES (n=20 lesions)	SS-SES (n=34 lesions)	CoCr-BMS (n=7 lesions)	P-value for CoCr-EES vs. SS-SES	P-value for CoCr-EES vs. CoCr-BMS
Distribution of neoatherosclerosis	n=20	n=34	n=7	0.74	0.92
Focal	11 (55%)	17 (50%)	4 (57%)		
Diffuse	9 (45%)	17 (50%)	3 (43%)		

Figure 6. Prevalence and type of neoatherosclerosis. A, Bar graph shows the prevalence and type of neoatherosclerosis. B, The data are shown in table form. C, Distribution of neoatherosclerosis is shown. *Tabular Fisher exact test was substituted because the generalized estimating equation fails as a result of low observed frequency in CoCr-EES. CoCr-BMS indicates cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; SS-SES, stainless steel sirolimus-eluting stent; TCFA, thin-cap fibroatheroma.

This process, called *neoatherosclerosis*, is accelerated by DESs relative to BMSs and may progress to cause plaque rupture and late stent thrombosis through mechanisms similar to native atherosclerosis. In a recent optical coherence tomography study of patients with very late stent thrombosis (>1 year from stent implantation), neoatherosclerosis was the second most common cause.[23] In our current study, the prevalence of neoatherosclerosis was significantly less with CoCr-EESs versus SS-SESs but was lowest with CoCr-BMSs, consistent with previous data.[11] An explanation for the reduced amount of neoatherosclerosis with CoCr-EESs versus SS-SESs might be the improved healing in the former, which may prevent the entrance of macrophages into the intimal space because the endothelial barrier surface may be more complete. Another possibility is that everolimus may interfere less with endothelial barrier function versus sirolimus, as we have shown in in vitro experiments.[24]

In this regard, BMSs had the best response, as only 20% of BMS samples had any evidence of neoatherosclerosis. We showed previously that mTOR (mammlian target of rapamycin) inhibitors such as sirolimus eluted from a DES interfere with endothelial barrier function through specific binding to FKBP12 (FK506 binding protein), which impairs barrier formation by activation of protein kinase C-α and downstream disruption of the p120–VE cadherin interaction.[25] It remains theoretically possible that polymer degradation in BP-DESs might return the endothelium back to normal function more quickly than DP-DESs because the persistent polymer in the latter promotes drug retention and prolonged impairment of barrier function. Our current data cannot fully explore this hypothesis because of the practical limitations in the timely collection of samples but suggest that further work focusing on this particular advantage of BP-DESs is needed.

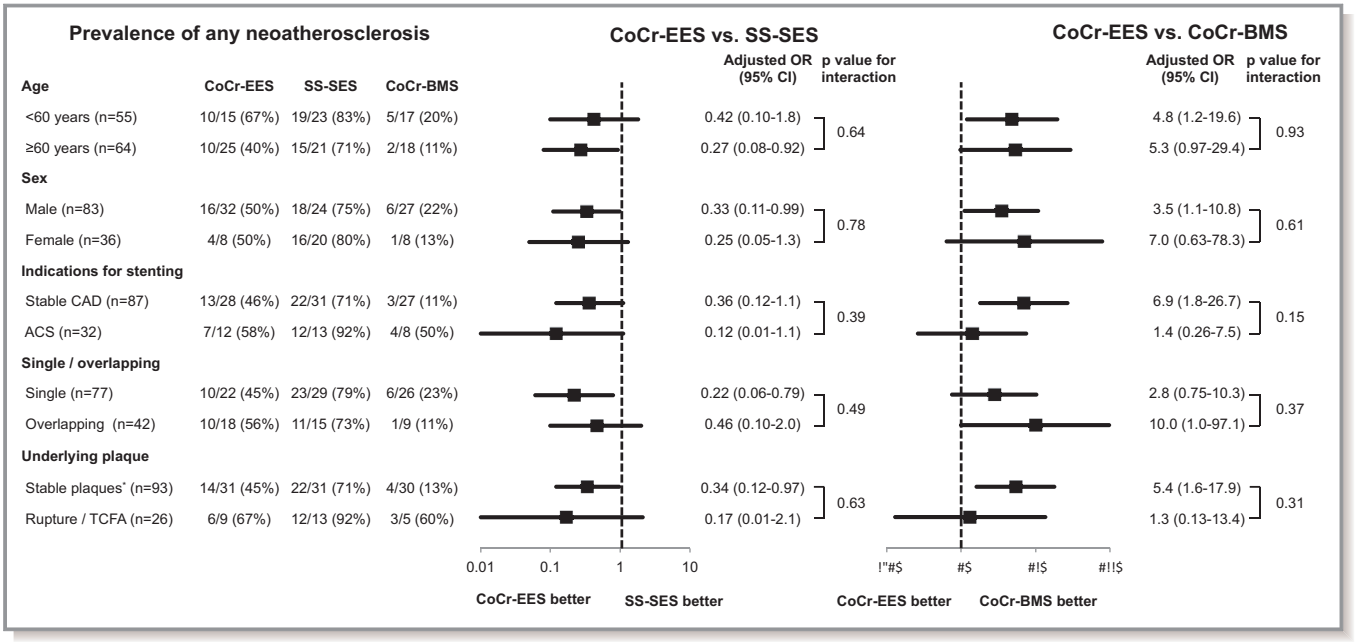


Figure 7. Subgroup analysis for the presence of any neoatherosclerosis with CoCr-EESs vs SS-SESs and CoCr-BMSs. Stable CAD include fibroatheroma, fibrocalcific plaque and pathological intimal thickening. ACS indicates acute coronary syndrome; CAD, coronary artery disease; CI, confidence interval; CoCr-BMS indicates cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; OR, odds ratio; SS-SES, stainless steel sirolimus-eluting stent; TCFA, thin-cap fibroatheroma.

Clinical Implications

Our data challenge the belief that the biocompatibility of bare metal surfaces is superior to those coated by DPs, which some data have shown are associated with some long-term inflammation that can lead to neointimal proliferation.[26] A recently published randomized clinical study (n=9013) comparing second-generation DESs (majority CoCr-EESs) and BMSs reported less target lesion revascularization (5.3% and 10.3%, respectively; $P<0.001$) at 6-year follow-up.[27] In

Table 4. List of Very Late Stent Thrombosis

No.	Stent Type	Age, y; Sex	Vessel	Prox/ Mid/Dist	Duration, y	Cause of Stent Thrombosis	Inflammation Score	Prevalence of >30% Uncovered Struts	Hypersensitivity Reaction
1	CoCr-EES	76; M	LAD	Prox	2.0	Uncovered strut	0	Yes	No
2	CoCr-EES	89; F	LCX	Prox	5.0	Embolization from prosthetic valve	0.5	No	No
3	SS-SES	59; M	RCA	Dist	1.9	In-stent plaque rupture	3.0	No	Yes
4	SS-SES	52; M	LAD	Mid	2.0	Neointimal erosion	2.5	No	No
5	SS-SES	51; M	LAD	Prox	1.0	Uncovered strut	2.4	Yes	No
6	SS-SES	67; F	LAD	Prox	3.4	Hypersensitivity reaction	3.7	Yes	Yes
7	SS-SES	61; M	RCA	Prox	3.0	In-stent plaque rupture	1.3	No	No
8	SS-SES	40; F	LAD	Prox	5.0	Neointimal erosion	0.4	No	No
9	SS-SES	39; F	LM		5.0	Hypersensitivity reaction	4.0	Yes	Yes
10	CoCr-BMS	30; F	RCA	Prox	5.0	In-stent plaque rupture	1.6	No	No
11	CoCr-BMS	36; M	LAD	Prox	5.0	In-stent plaque rupture	1.3	No	No
12	CoCr-BMS	56; M	RCA	Dist	5.0	In-stent plaque rupture	1.6	No	No

CoCr-BMS indicates cobalt–chromium bare metal stent; CoCr-EES, cobalt–chromium everolimus-eluting stent; Dist, distal.; F, female; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; M, male; Mid, middle; Prox, proximal; RCA, right coronary artery; SS-SES, stainless steel sirolimus-eluting stent.

contrast, when SS-SESs were compared with BMSs in another registry, the cumulative incidence of clinically driven target lesion revascularization was numerically similar at 7-year follow-up (10.6% versus 10.2%, respectively).[28] Differences in target lesion revascularization between the 2 stents became less apparent over time, suggesting that SESs suffered from a late catch-up phenomenon that has also been seen in other studies.[29] Conversely, it appears that late catch-up seems less pronounced with CoCr-EESs than with SS-SESs.[4] Still, it is important to keep in the mind that neoatherosclerosis, which is another important factor for late events, occurred least with BMSs.

This study may have important implications for newer generation DESs, especially those with BPs, as these will become BMSs after polymer degradation is complete. From current available clinical data, no difference for target lesion failure has been observed between CoCr-EESs and newer generation BP-DESs.[30–32] The benefits of BP-DESs are believed to occur a long time after polymer degradation is complete because the stents were made based on the assumption that the bare surface of the metal would be more biocompatible than a permanent polymer. Our data challenge this assumption by demonstrating that BMSs are also associated with some long-term inflammation, although the clinical consequences of this remain unknown.

Study Limitation

Because this is an autopsy study, the findings may not be representative of patients who receive stents and survive. Highly detailed clinical information such as the status of antiplatelet therapy information was not always available for every case, as we received samples from multiple centers all over the world. Nevertheless, this study provides important information that cannot be obtained through clinical studies. The design of this type of pathology registry includes substantial biases that preclude conclusive comparative analyses between devices. Nonetheless, the type of studies conducted by our group has been important in furthering our understanding of the vascular responses to DESs in humans.

Conclusion

Our results suggest that the response to each type of stent (even those within the same category) is highly specific and should not be generalized. The response with CoCr-EESs was favorable from the standpoint of intimal suppression, healing, and inflammation. BMSs showed distinct advantages in terms of neoatherosclerosis development. Our data suggest distinct advantages for both DP-DESs with fluoropolymer coating and for BMSs. Further clinical data are needed to determine whether the distinct vascular responses shown in our study for each type of system results in clinical advantages.

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SUPPLEMENTAL MATERIAL

Table S1. Pathological assessment in the lesions without TLF

	CoCr-EES (n=36)	SES (n=31)	BMS (n=17)	P-value for CoCr-EES vs. SS-SES	P-value for CoCr-EES vs. CoCr-BMS
No. of histologic section evaluated	n=237 sections	n=214 sections	n=91 sections		
No. of stent struts evaluated	n=2849 struts	n=2088 struts	n=1047 struts		
External elastic lamina area, mm^2	13.0 [11.7-15.4]	13.4 [9.5-17.5]	12.6 [9.0-14.1]	0.99	0.19
Internal elastic lamina area, mm^2	11.8 [10.6-14.1]	12.3 [8.3-15.7]	11.4 [8.1-12.7]	0.87	0.17
Stent area, mm^2	7.2 [5.2-8.1]	7.2 [5.6-9.4]	6.0 [4.7-7.3]	0.86	0.02
Underlying plaque area, mm^2	5.0 [3.3-6.0]	4.4 [2.7-6.6]	5.0 [2.8-6.8]	0.70	0.82
Mean neointimal area, mm^2	1.2 [0.8-1.6]	0.9 [0.6-1.3]	1.7 [1.5-1.9]	0.01	0.08
Mean neointimal thickness, mm	0.16 [0.12-0.24]	0.15 [0.10-0.21]	0.32 [0.25-0.37]	0.14	<0.01
Maximum neointimal thickness, mm	0.31 [0.22-0.47]	0.27 [0.20-0.41]	0.47 [0.39-0.61]	0.34	0.01
Mean percentage of uncovered struts per lesion, %	0 [0-2.4]	2.9 [0-7.5]	0 [0-0]	0.045	<0.01
Rate of lesions of >30% uncovered struts†, n (%)	2 (6%)	8 (26%)	0	0.02	
Percentage of strut with fibrin, %	0 [0-5.4]	2.4 [0-7]	0 [0-3.7]	0.15	0.10
Inflammation score	0.6 [0.3-0.8]	1.4 [1-2.3]	1.0 [0.4-1.2]	<0.01	0.14
Mean percentage of struts with giant cells per lesion, %	4.1 [1.0-8.8]	15.1 [2.2-23.2]	4.7 [0-14.5]	<0.01	0.43
Maximum number of eosinophils per strut*	0 [0-0.3]	0.4 [0-1.9]	0.2 [0-0.5]	<0.01	0.30
Rate of hypersensitivity reaction†, n (%)	0	4 (13%)	0	<0.01	
Neovascularization score	0.5 [0.2-1.4]	0.7 [0-1.9]	1.0 [0.4-1.9]	0.65	0.06

CoCr-EES, cobalt-chromium everolimus-eluting stent; SS-SES, sirolimus eluting-stent; CoCr-BMS, cobalt-chromium bare metal stent

* Tabular Fisher exact test was substituted because GEE fails due to low observed frequency.

† Poisson loglinear model was selected.