Neoaterosclerosis.
La enfermedad del stent

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REVIEW

Imaging

Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment

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Introducción

- Enfermedad arterial coronaria (CAD) como primera causa de mortalidad a nivel mundial. Unos 7.2 millones de muertes anuales.

- La ICP revolucionó el tratamiento de pacientes con CAD.

- Los DES tratan exitosamente la proliferación neointimal dentro del segmento stentado.

- La inhibición del crecimiento neointimal por fármacos antiproliferativos produce retraso de la curación vascular.

Introducción

- Incremento de incidencia acumulada con los DES de 1ª gen en trombosis de stent tardía y muy tardía.

- Reducción de riesgo de trombosis tardía con la 2ª gen DES manteniendo eficacia antirestenótica.

- Persiste fallo tardío del stent incluso con los DES actuales. Ensayos clínicos actuales muestran incremento de incidencia acumulada de TVR en todas las generaciones de DES.

Introducción

- Falta de cobertura de struts en DES 1ª gen , retraso de curación arterial, como sustrato patológico para LST /VLST.

- Otros factores se asocian con el fallo tardío del DES: reacción hipersensibilidad, malaposición con depósito de fibrina, fractura del stent, neoaterosclerosis intrastent.

- Incidencia de neoaterosclerosis se incrementa con el tiempo post-implante, aparece más precoz y frecuentemente en DES 1ªgen que en BMS.

- A pesar de la mejora con la 2ªgen DES los ensayos no muestran una menor prevalencia de neoaterosclerosis respecto a los DES 1ª gen.

Introducción

- La prevalencia de neoaterosclerosis está por determinar con los DES actuales.
- La detección precoz con las actuales técnicas de imagen facilita el tratamiento específico para alterar su historia natural y prevenir complicaciones (VLST y restenosis tardía intrastent).

Neoaterosclerosis intrastent. Características morfológicas

- Acúmulo de macrófagos espumosos cargados de lípidos.
- Con /sín core necrótico.
- Con /sín calcificación de la neoíntima.
- Sin continuidad entre la lesión dentro de la neoíntima y la aterosclerosis nativa de base.
- Dato más precoz: grupos de macrófagos espumosos, frecuentemente en área peristrut o cerca de la superfície luminal.

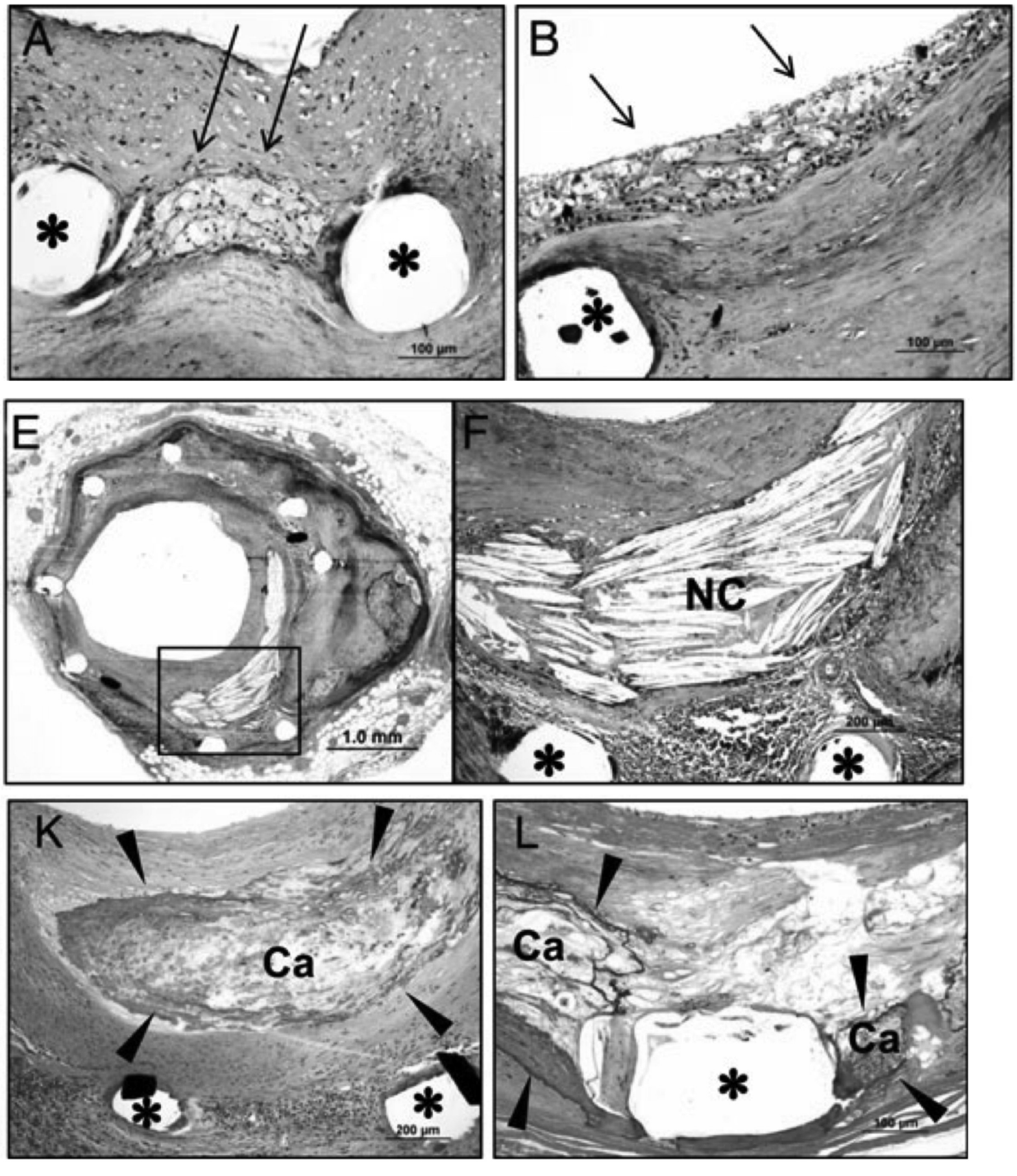
Neoaterosclerosis intrastent. Características morfológicas

- Acúmulo de macrófagos progresa para formar un fibroateroma, en la superficie luminal o dentro de la neoíntima.

- La infiltración de macrófagos en la neoíntima forma un fibroateroma de cápsula fina que puede llevar a la rotura de placa.

- Ocasionalmente el core necrótico puede mostrar hemorragia por fisura o rotura de la superficie luminal o por fuga desde los vasa vasorum de la adventicia.

- Calcificación dentro de la neoíntima con el paso del tiempo post-implante. Por apoptosis celular o calcificación de material extra celular.



Componentes de la neoaterosclerosis

Potenciales mecanismos de neoaterosclerosis acelerada.

- Aterosclerosis en arteria coronaria nativa se desarrolla en décadas.

- Neoaterosclerosis intrastent se desarrolla en meses o pocos años tras el implante, y más rápida y frecuentemente en DES que en BMS.

- Se desconoce con certeza el mecanismo responsable que acelera el proceso, se postula por el endotelio incompetente y disfuncionante tras implantar el stent (más frecuente en DES que en BMS por efecto de fármacos antiproliferativos).

Potenciales mecanismos de neoaterosclerosis acelerada.

- Pérdida de función de barrera del endotelio. Entrada de lipoproteinas al espacio subendotelial.

- La presencia de neoaterosclerosis tras BMS sugiere que hay otros mecanismos asociados más allá de fármacos antiproliferativos.

  - Alteraciones del flujo sanguíneo local tras implante de stent favorecen depósito de macrófagos (células espumosas).

  - Formación de trombo tras implante de stent, que se resuelve pero persiste fibrina peristrut.

  - Polímero de los DES favorece la inflamación crónica y promueve el desarrollo de neoaterosclerosis.

  - Apoptosis de macrófagos y células de músculo liso favorecen core necrótico.

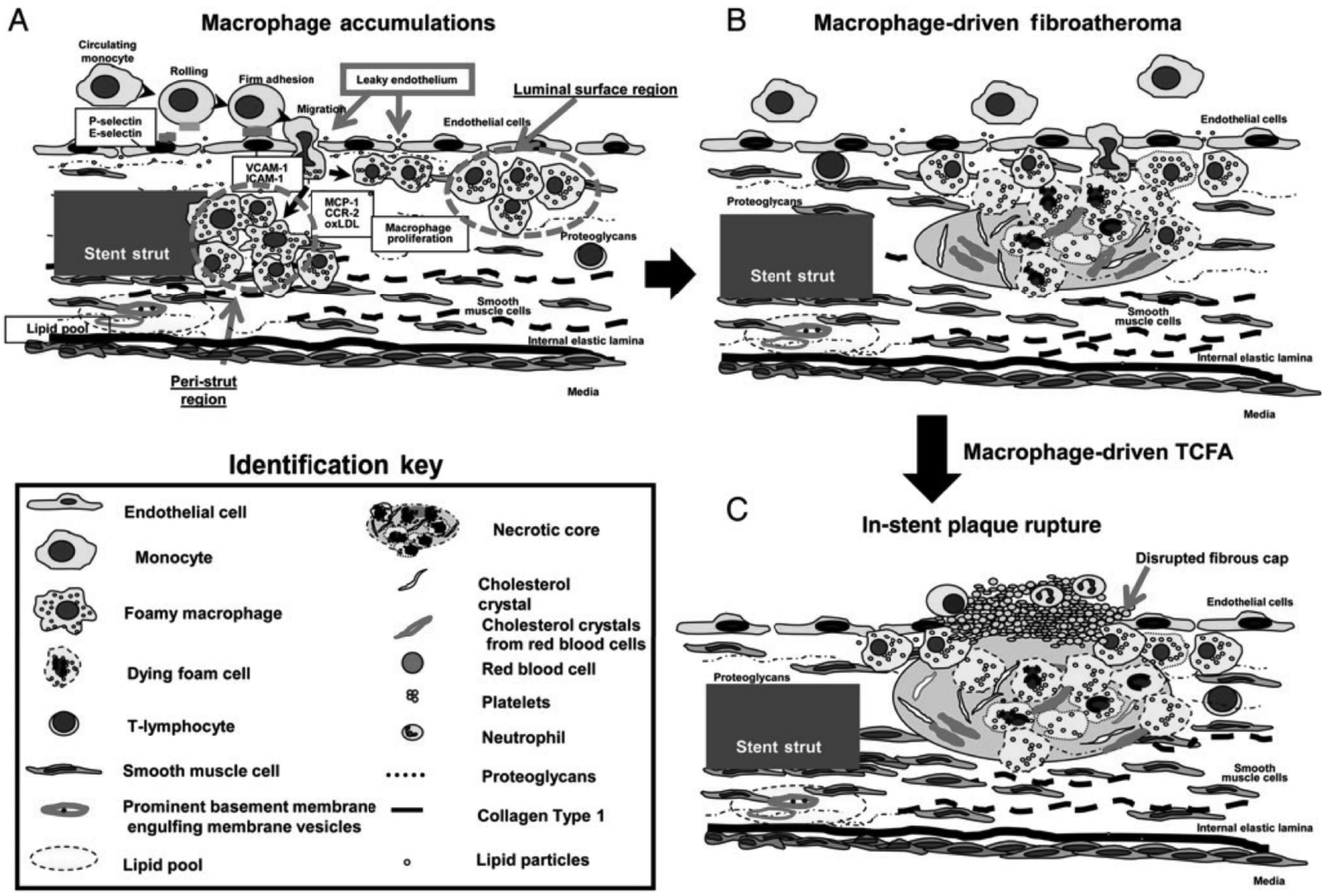
  - En neoaterosclerosis hay más necrosis y menos carga lipídica, lo que favorece la rotura de placa intrastent.

Potenciales mecanismos de neoaterosclerosis acelerada.

- DES implantados sobre lesiones inestables generan mayor retraso de curación vascular que sobre lesiones estables.

- Gran mayoría de placas neoateroscleróticas se originan dentro del stent implantado, sin ser continuación de placas adyacentes a los bordes del stent ni penetración de la placa tratada con stent dentro de éste.

- La neoaterosclerosis presenta placas más frágiles al carecer de células de músculo liso , y por tanto tener el core necrótico más cercano a la luz del vaso.


A
Macrophage accumulations
Circulating monocyte
Rolling
Firm adhesion
Leaky endothelium
Luminal surface region
Migration
P-selectin
E-selectin
Endothelial cells
VCAM-1
ICAM-1
MCP-1
CCR-2
oxLDL
Macrophage proliferation
Proteoglycans
Stent strut
Smooth muscle cells
Lipid pool
Internal elastic lamina
Peri-strut region
Media
B
Macrophage-driven fibroatheroma
Endothelial cells
Proteoglycans
Stent strut
Smooth muscle cells
Internal elastic lamina
Media
Macrophage-driven TCFA
C
In-stent plaque rupture
Disrupted fibrous cap
Endothelial cells
Proteoglycans
Stent strut
Smooth muscle cells
Internal elastic lamina
Media
Identification key
Endothelial cell
Monocyte
Foamy macrophage
Dying foam cell
T-lymphocyte
Smooth muscle cell
Prominent basement membrane engulfing membrane vesicles
Lipid pool
Necrotic core
Cholesterol crystal
Cholesterol crystals from red blood cells
Red blood cell
Platelets
Neutrophil
Proteoglycans
Collagen Type 1
Lipid particles

Prevalencia de neoaterosclerosis

- La aparición de datos de neoaterosclerosis es más precoz en DES que en BMS (70 d PES, 120 d SES y 900 días BMS).

- Datos de inestabilidad de la placa aparecen sobre los 2 años tras implante en DES 1ª gen y 5 años en BMS.

- Hasta los 3 años, los datos de necropsias muestran prevalencia comparable de neoaterosclerosis entre 1ª y 2ª gen de DES.

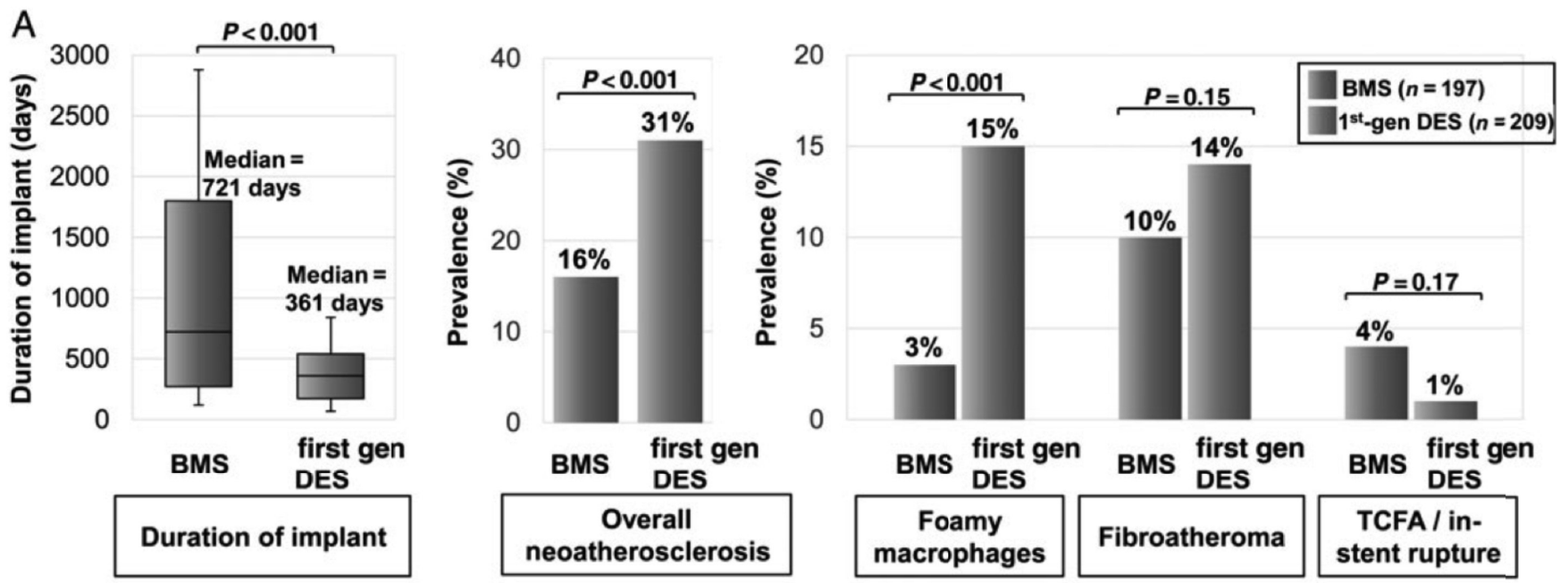


Figure 3 Prevalence and characteristics of neoatherosclerosis in human autopsy analyses. (*A*) Despite the shorter duration of implant in first-generation drug-eluting stents when compared with bare metal stent, first-generation drug-eluting stents showed greater prevalence of neoatherosclerosis, particularly those characterized by foamy macrophage clusters. (*B*) Observed frequency of neoatherosclerosis in second-generation cobalt-chromium everolimus-eluting stents was comparable with the first-generation sirolimus-eluting stent and paclitaxel-eluting stent. (*A*) is reproduced with permission from Ref.[20] and (*B*) is reproduced with permission from Ref.[22]

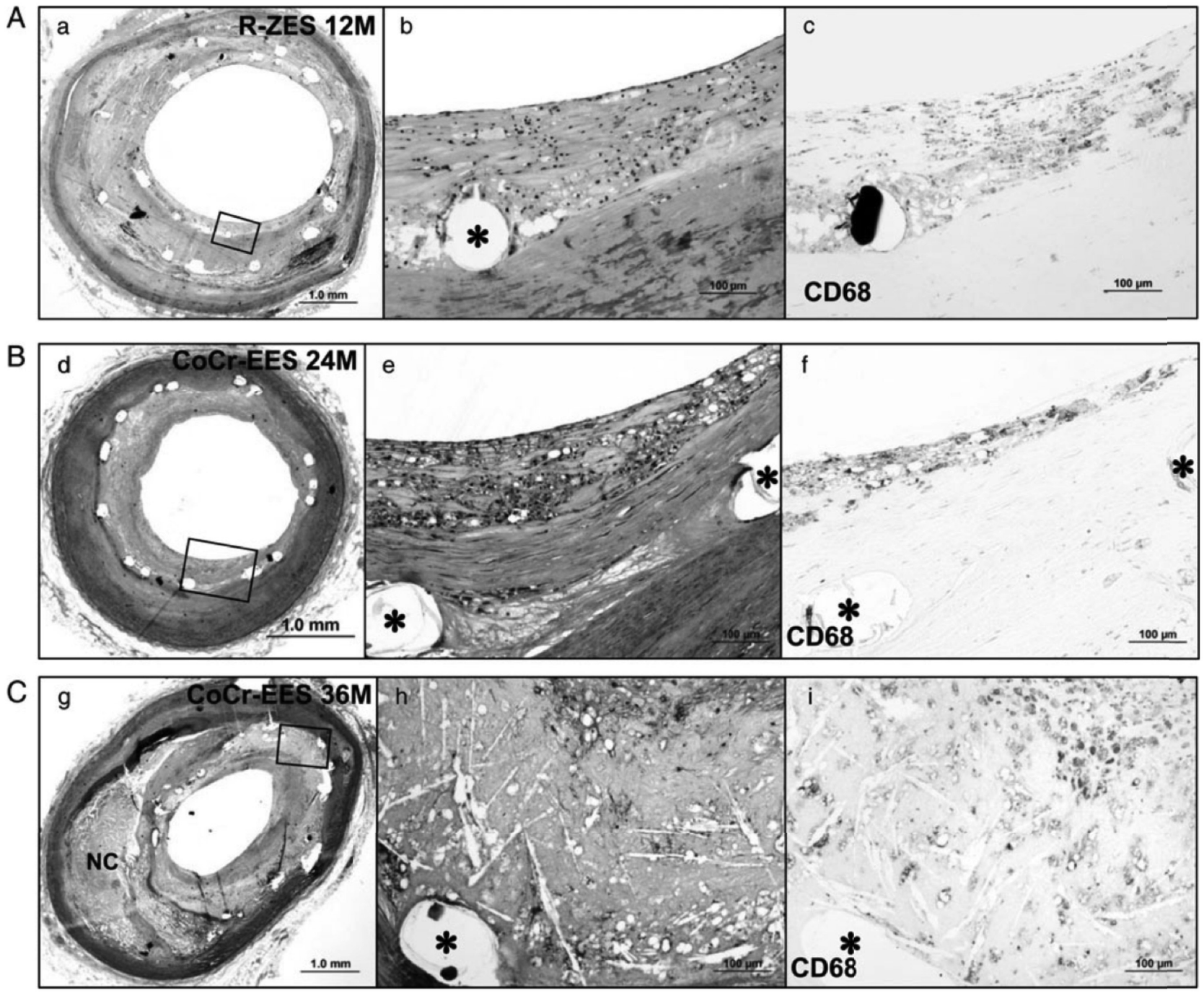


Figure 4 Representative histologic images showing neoatherosclerosis in second-generation drug-eluting stents. (*A*) Foamy macrophage clusters in Resolute zotarolimus-eluting stent. (*B*) Foamy macrophage accumulation in cobalt-chromium everolimus-eluting stents. (C) Fibroatheroma developed within cobalt-chromium everolimus-eluting stents. The presence of foamy macrophages was confirmed by immunostaining using an anti-CD68 antibody. *Stent strut. (*B*) and (*C*) are reproduced with permission from Ref.[22]

Neoaterosclerosis en fallo tardío del stent.

- Fallo tardío del stent (LST, VLST y restenosis tardía intrastent) aparece como un factor importante tras el implante de DES y BMS.

- Se recogen datos de autopsias sobre 614 lesiones tratadas con stent.

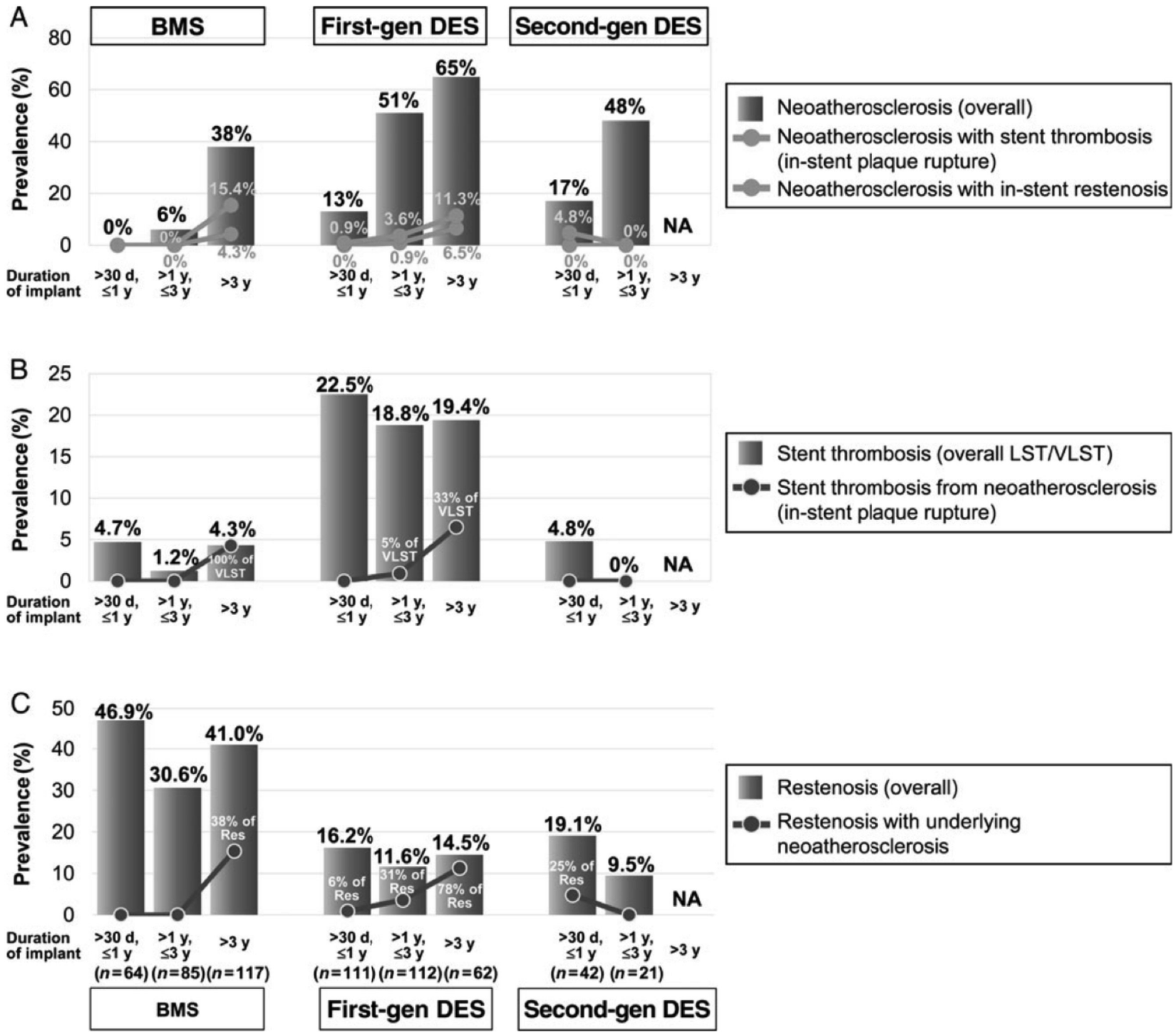
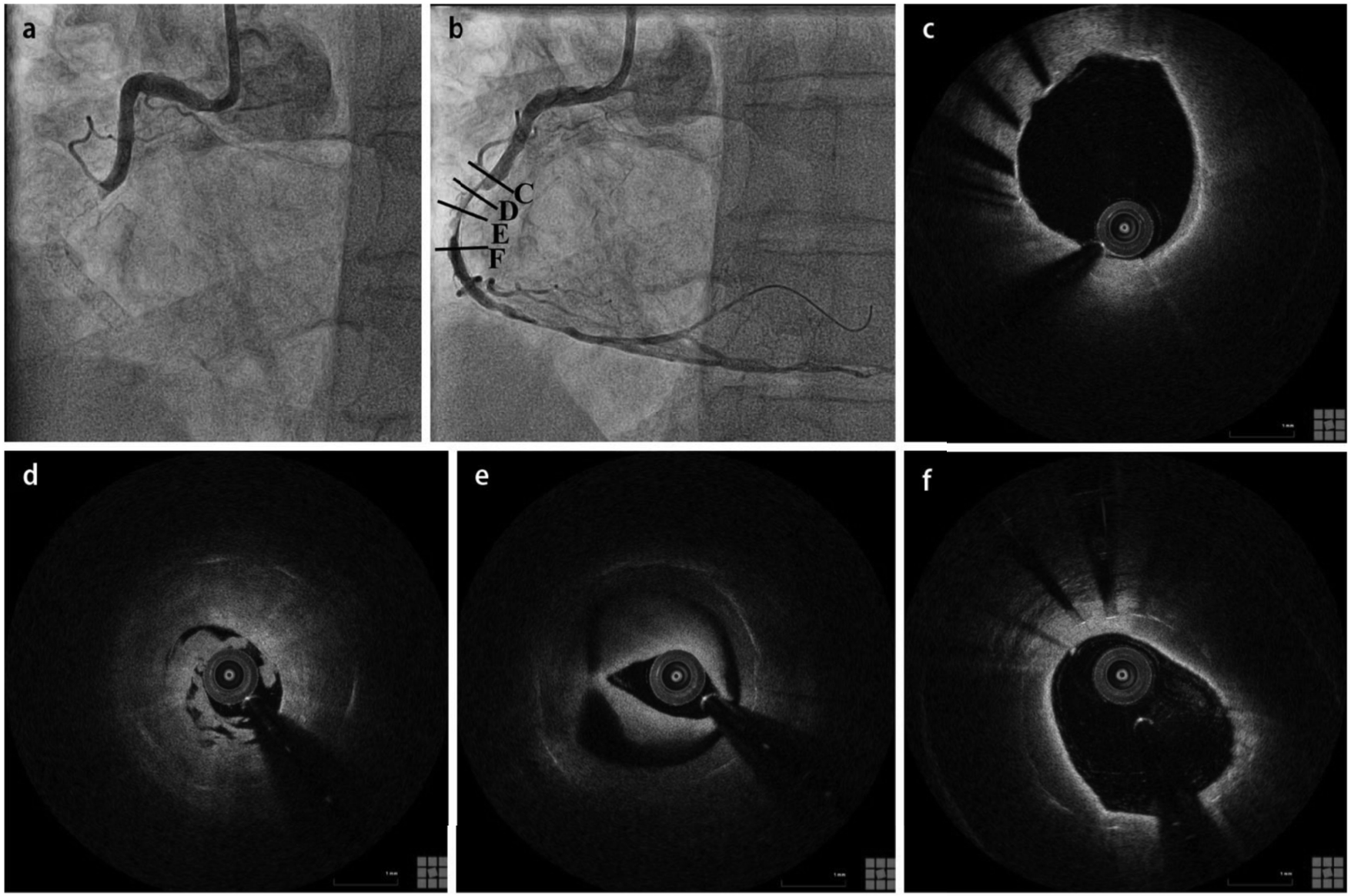


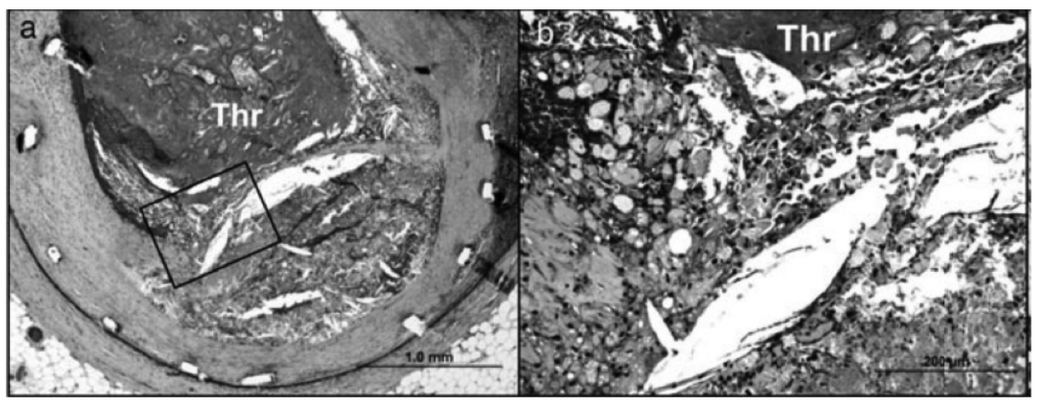
Figure 5 (*A*) Prevalence of neoatherosclerosis in bare metal stent, first- and second-generation drug-eluting stents stratified by duration of implant (bar graphs) along with the prevalence of restenosis (green line) and thrombosis (orange line) in the lesions with neoatherosclerosis and late stent failure. (*B*) Prevalence of overall stent thrombosis, in association with neoatherosclerosis (in-stent plaque rupture). (*C*) Prevalence of in-stent restenosis and its association with underlying neoatherosclerosis. LST/VLST, late and very late stent thrombosis; Res, restenosis.

Neoaterosclerosis en fallo tardío del stent.

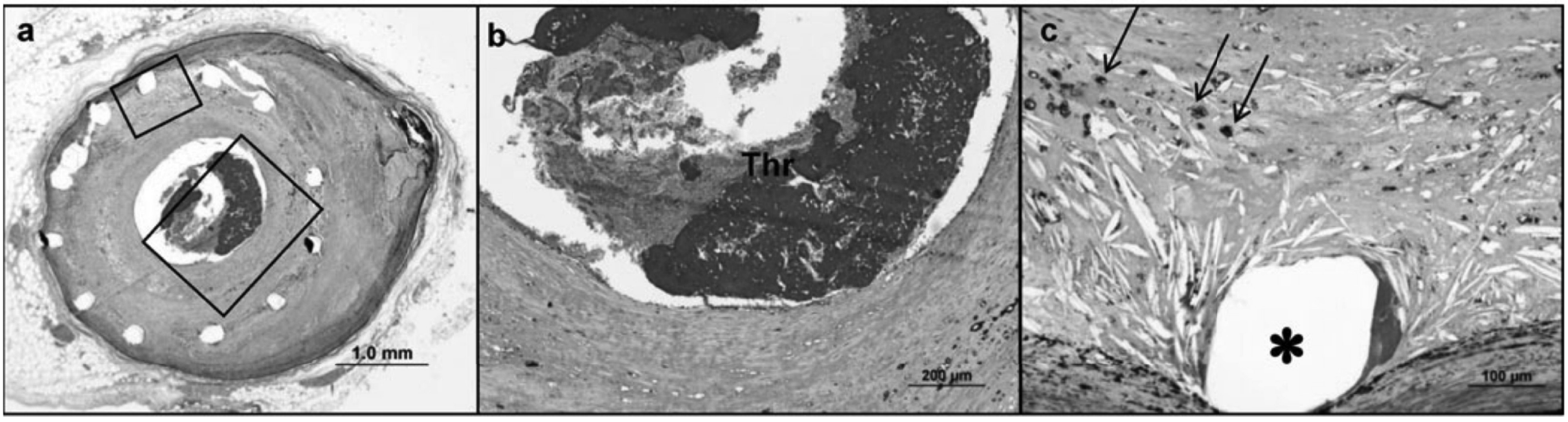
- Sobre VLST:
  - A tres años del implante todos los casos en BMS se atribuyen a neoaterosclerosis y el 33% de los DES 1ª gen.
  - Otra causa de VLST en 1ª gen DES se asocian a struts no cubiertos y reacciones de hipersensibilidad al polímero.
- Se plantea como otra causa de VLST la erosión neointimal sin estar asociada a neoaterosclerosis.

VLST debida a rotura de placa en neoaterosclerosis





VLST con erosión neointimal sin neoaterosclerosis



Neoaterosclerosis en fallo tardío del stent.

- Neoaterosclerosis con restenosis intrastent de base, fue más frecuente en BMS, seguida de 1ª gen DES y menos frecuentes en 2ª gen DES.

- Clara diferencia en el tiempo de aparición tras el implante del stent.

  - Más precoz en DES 1ªgen que en BMS, y aumento de ambos con el tiempo. Faltan datos para valorar la 2ª gen de DES.

- Hallazgos de autopsias muestran relación entre neoaterosclerosis y restenosis intrastent, pero no se puede establecer papel causal de la neoaterosclerosis.

- Se postulan dos mecanismos sobre la placa neoaterosclerótica:

  - Rotura de la placa y formación de trombo oclusivo (VLST).

  - Rotura de la placa que se sella(“curación”) con infiltración e colágeno y proteoglicanos (restenosis intrastent). Puede evolucionar a la CTO .

Restenosis tardía debida a neoaterosclerosis

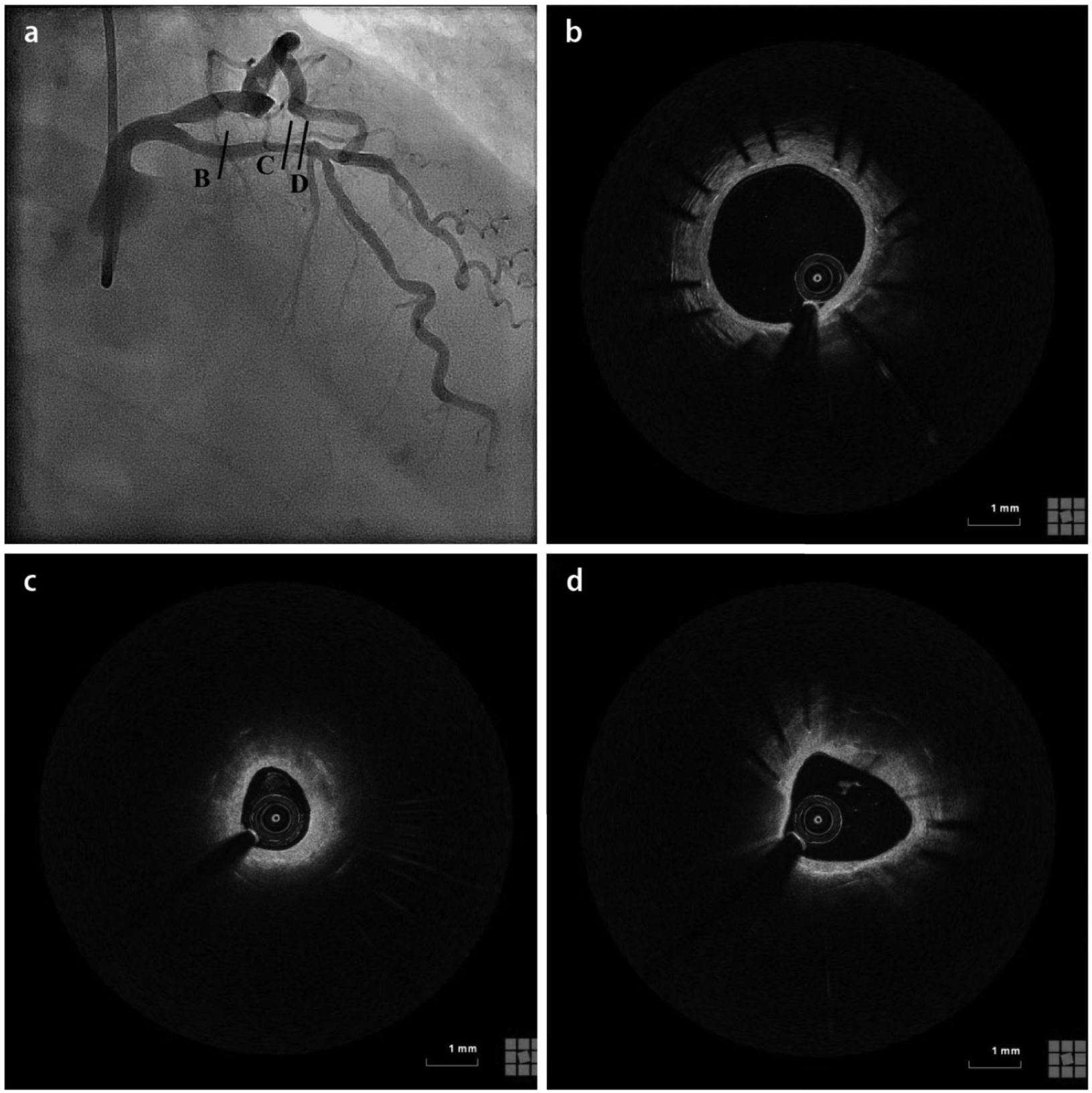
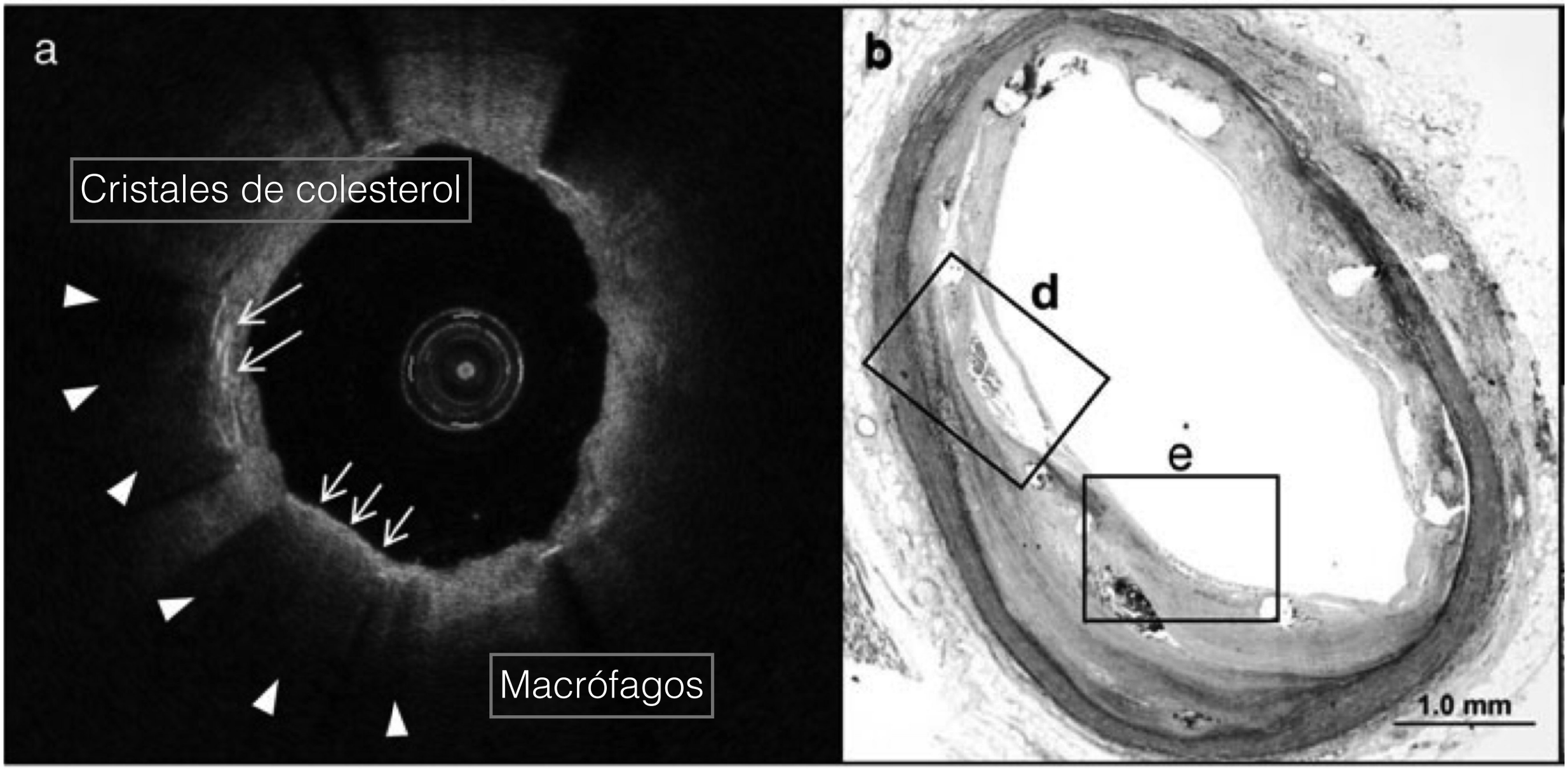
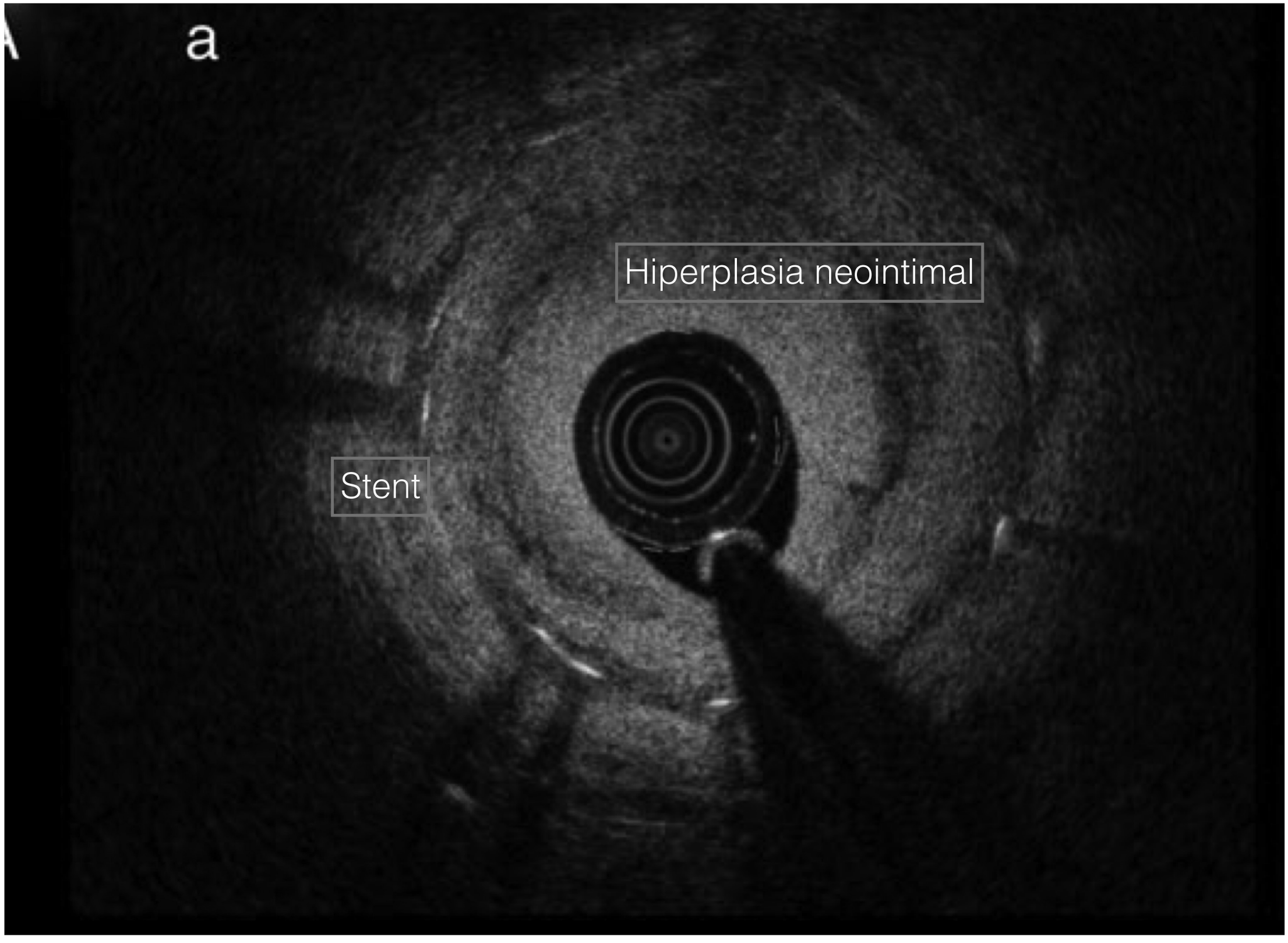


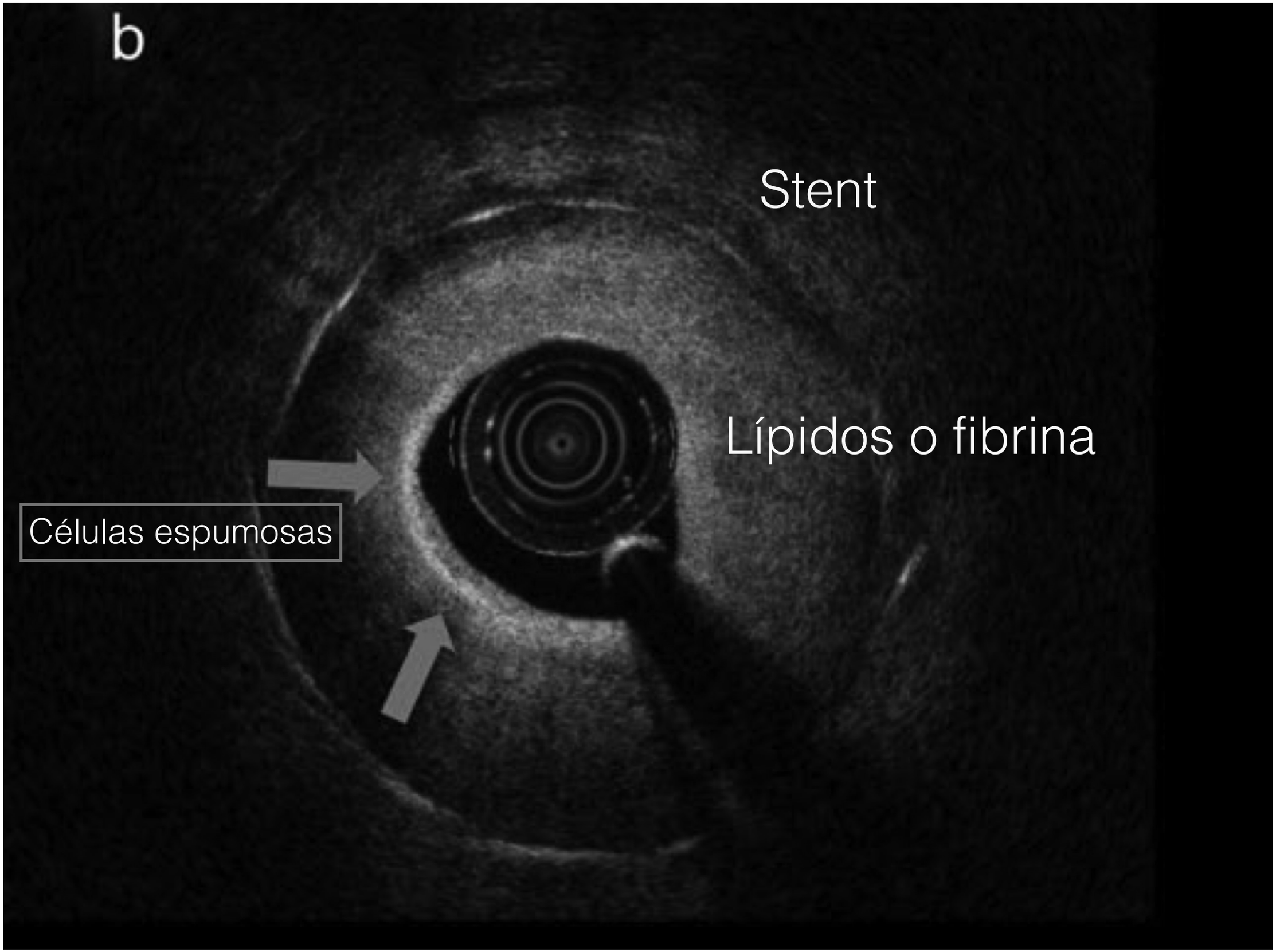
Imagen intravascular de neoaterosclerosis.

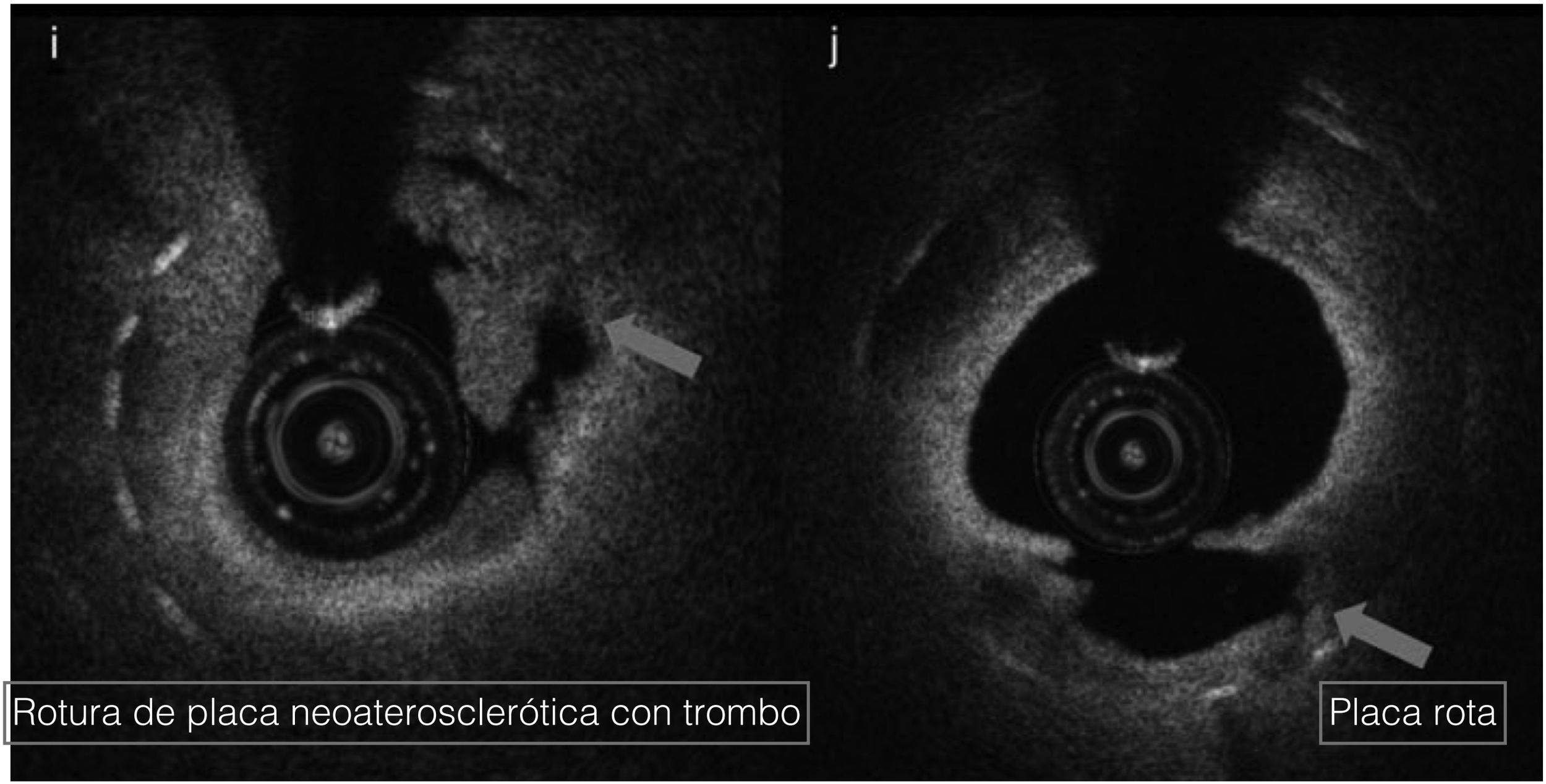
- Técnicas de utilidad:
  - Angioscopia: sólo permite imagen superficial de la placa.
  - IVUS: limitado para caracterización titular por insuficiente resolución espacial (150 - 250 micras).
  - OCT: mayor resolución (10-20 micras) que permite la caracterización del tejido neointimal dentro del stent.

Lesión coronaria estentada con neoaterosclerosis




a
Hiperplasia neointimal
Stent


b
Stent
Lípidos o fibrina
Células espumosas


i
j
Rotura de placa neoaterosclerótica con trombo
Placa rota

Implicaciones clínicas

- Actualmente el uso de DES se ha expandido por su eficacia y seguridad demostradas a largo plazo.

- Aparición reciente del concepto de neoaterosclerosis (mejora en las técnicas de imagen que permiten detectarla), con mayor progresión y frecuencia en DES que en BMS.

- Implicación en el fallo tardío de stent.

- Aún por definir factores predisponentes y tratamientos preventivos para la aparición de ésta.

Predictors for Neoatherosclerosis

A Retrospective Observational Study From the Optical Coherence Tomography Registry

Taishi Yonetsu, MD; Koji Kato, MD, PhD; Soo-Joong Kim, MD, PhD; Lei Xing, MD; Haibo Jia, MD, PhD; Iris McNulty, RN; Hang Lee, PhD; Shaosong Zhang, MD, PhD; Shiro Uemura, MD, PhD; Yangsoo Jang, MD, PhD; Soo-Jin Kang, MD, PhD; Seung-Jung Park, MD, PhD; Stephen Lee, MD; Bo Yu, MD, PhD; Tsunekazu Kakuta, MD, PhD; Ik-Kyung Jang, MD, PhD

Background—Recent studies have reported development of neoatherosclerosis (NA) inside the stents several years after stent implantation. The aim of this study was to determine the predictors for NA using optical coherence tomography.

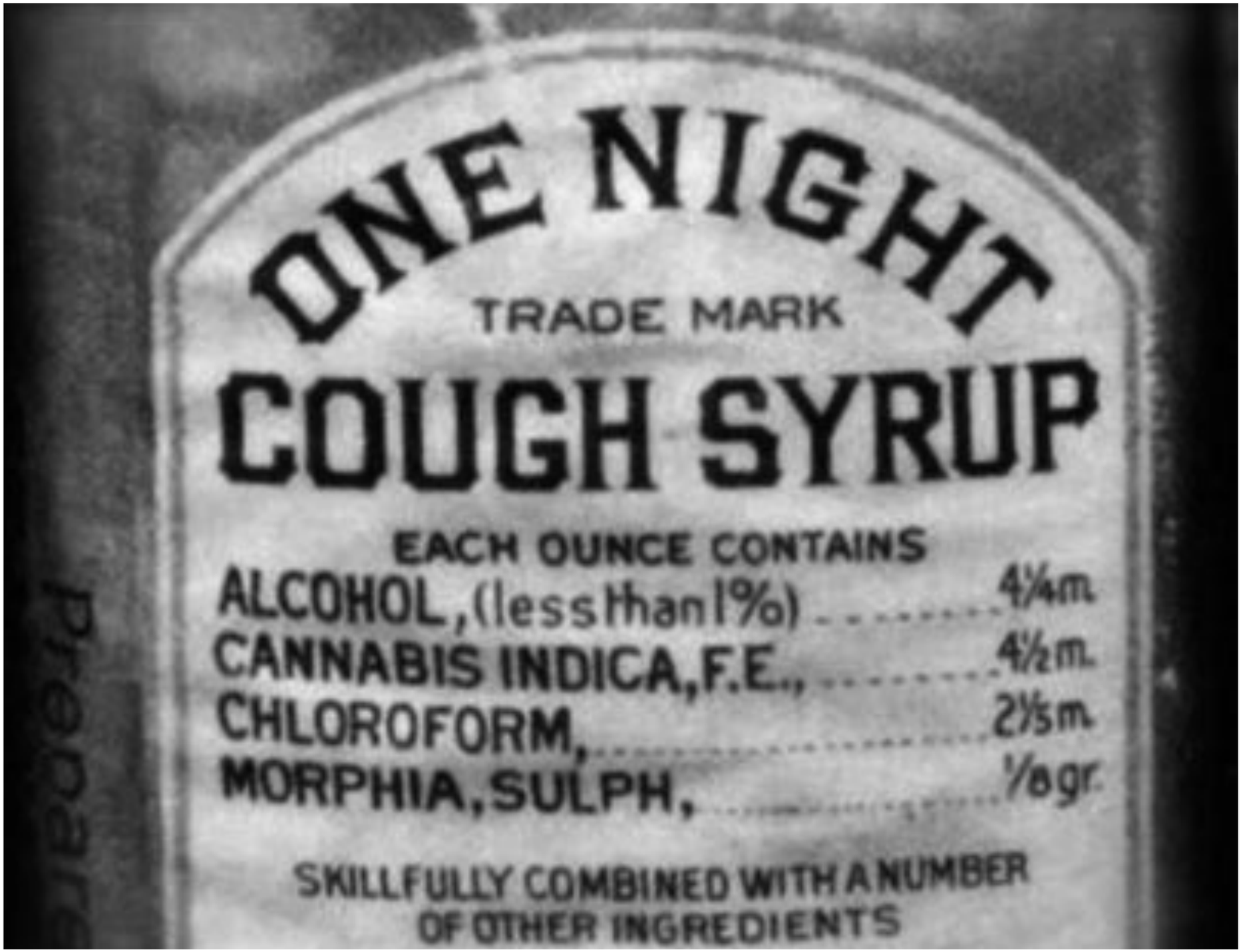
Methods and Results—From a total of 1080 patients who underwent optical coherence tomography, we identified 179 stents in 151 patients in which the mean neointimal thickness was >100 μm. The presence of lipid-laden neointima or calcification inside the stents was defined as NA in the present study. Patient characteristics, stent type, and time since stent implantation (stent age) were compared between stents with or without NA. Univariable and multivariable logistic regression analyses were used to assess the independent predictors. In univariate analysis, stent age ≥48 months (Odds ratio [OR], 4.48; [95% CI 2.68-9.65]; $P<0.001$), drug-eluting stents (OR, 2.66; [95% CI, 1.38–5.16]; $P=0.004$), age ≥65 years (OR, 1.91; [95% CI, 1.05–3.44]; $P=0.032$), current smoking (OR, 2.30; [95% CI, 1.10–4.82]; $P=0.024$), chronic kidney disease (OR, 4.17; [95% CI, 1.42–12.23]; $P=0.009$), and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockade use (OR, 0.42; [95% CI, 0.22–0.80]; $P=0.008$) were significant predictors. In multivariate analysis, stent age ≥48 months, all subtypes of drug-eluting stent, current smoking, chronic kidney disease, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockade use remained independent predictors for NA.

Conclusions—In addition to the stent type and the stent age, patient characteristics, including current smoking, chronic kidney disease, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockade, were associated with the presence of NA. This result may support the importance of secondary prevention after stent implantation. **(*Circ Cardiovasc Imaging*. 2012;5:660-666.)**

Table 3. Predictors for Neoatherosclerosis

	Univariate Models			First Multivariate Model (n=155)			Final Multivariate Model (n=179)		
	Odds Ratio	95% CI	*P*	Adjusted Odds Ratio	95% CI	*P*	Adjusted Odds Ratio	95% CI	*P*
Stent age >48 mo	4.48	2.08–9.65	<0.001	12.27	3.78–39.98	<0.001	10.45	3.71–29.41	<0.001
DES	2.66	1.38–5.16	0.004						
SES	2.47	1.21–5.05	0.013	4.08	1.28–13.05	0.018	3.86	1.44–10.38	0.007
PES	7.83	2.33–26.24	<0.001	21.08	5.60–79.43	<0.001	24.17	6.02–97.02	<0.001
ZES	3.34	0.98–11.34	0.053	5.58	1.12–27.70	0.036	7.18	1.51–34.21	0.013
EES	1.13	0.37–3.46	0.819	8.22	1.49–45.47	0.016	6.46	1.65–25.34	0.007
BMS	1.00	…	…	1.00	…	…	1.00	…	…
Age>65 y	1.91	1.05–3.44	0.032	2.69	1.13–6.37	0.025	1.84	0.85–3.97	0.121
Hypertension	1.29	0.68–2.44	0.443	2.40	0.86–6.68	0.093	1.87	0.77–4.52	0.166
Hyperlipidemia	0.94	0.49–1.79	0.849	0.94	0.32–2.74	0.915	1.01	0.39–2.61	0.982
Diabetes mellitus	1.63	0.86–3.09	0.134	1.33	0.56–3.16	0.513	1.12	0.53–2.43	0.765
Smoking	2.30	1.10–4.82	0.024	9.91	3.12–31.50	<0.001	7.03	2.46–20.04	<0.001
LDL-C>100 mg/dL	1.59	0.80–3.18	0.183	1.29	0.50–3.31	0.593			
TG>150 mg/dL	1.26	0.67–2.37	0.482	1.03	0.38–2.76	0.954			
CKD	4.17	1.42–12.23	0.009	3.76	1.03–13.65	0.044	3.69	1.10–12.35	0.035
Statin use	0.45	0.17–1.13	0.090	0.65	0.18–2.32	0.511	0.46	0.14–1.55	0.213
ACE-I/ARB use	0.42	0.22–0.80	0.008	0.42	0.16–1.12	0.083	0.39	0.17–0.91	0.028

(*Circ Cardiovasc Imaging*. 2012;5:660-666.)


ONE NIGHT
TRADE MARK
COUGH SYRUP
EACH OUNCE CONTAINS
ALCOHOL, (less than 1%) ..... 4¼m.
CANNABIS INDICA, F.E., ... 4½m.
CHLOROFORM, ... 2⅓m.
MORPHIA, SULPH, ... ⅛gr.
SKILLFULLY COMBINED WITH A NUMBER
OF OTHER INGREDIENTS

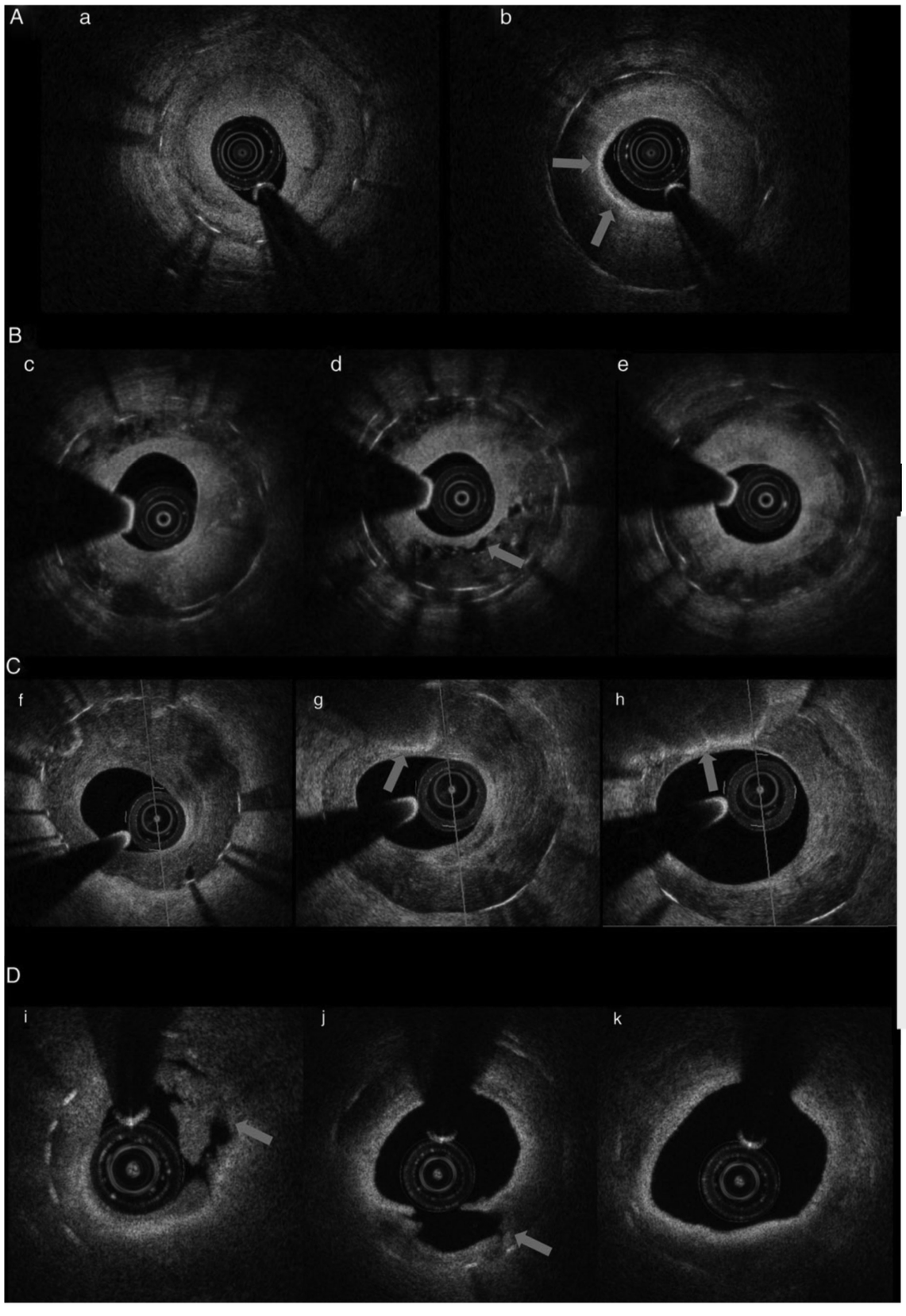


Figure 9 Clinical assessment of stented coronary arteries by optical coherence tomography showing variety of neointimal tissues. (*A*) A 55-year-old male patient presented with unstable angina 9 years after left anterior descending artery stenting with a durable polymer paclitaxel-eluting stent. Optical coherence tomography imaging revealed diffuse high-grade in-stent restenosis of the stented segment. Cross-sectional analysis of the distal stented segment (a) shows homogeneous high signal intensity close to the luminal surface with signal poor region in the middle of the neointima. This may be represent neointimal hyperplasia with smooth muscle cell growth and accumulation of lipid or extracellular matrix such as proteoglycan, or healed lesion secondary to thrombotic event. The proximal stented segment (b) shows an area of plaque with superficial high signal intensity (arrows), which may represent foamy macrophages accumulation. Deep to this, there is high signal attenuation which may indicates granulation tissue or the accumulation of lipid or fibrin. (*B*) Focal recurrent in-stent restenosis 4 years after durable polymer sirolimus-eluting stent implantation for in-stent restenosis in the proximal right coronary artery (RCA). Optical coherence tomography imaging confirmed focal restenosis with otherwise satisfactory result in the stented segment. Cross-sectional images of the restenotic area show heterogeneous and layered pattern tissue (c–e). The relatively well-demarcated borders and the lack of signal attenuation (d) suggest that this is unlikely to represent lipid-rich neoatherosclerosis but is likely granulation tissue with overlying neointimal hyperplasia rich in smooth muscle cells. Focal areas of signal dropout (arrow in d) likely represent neovascularization. (*C*) A 58-year-old male patient presented with stable angina 7 months after implantation of a durable polymer everolimus-eluting stent. Optical coherence tomography imaging showed focal in-stent restenosis. Cross-sectional analysis shows heterogeneous signal intensity in the neointima with relatively low attenuation (f–h). Such appearances may represent proteoglycan-rich neointima but another possibility includes granulation tissue or fibrin deposition. The middle (g) and the proximal (h) sections show focal signal rich region with attenuation (arrows) that indicate neoatherosclerosis characterized by foamy macrophage clusters. (*D*) A 67-year-old patient presented with stent thrombosis in the RCA 3 years after implantation of a durable polymer drug-eluting stents. Optical coherence tomography imaging after thrombus aspiration revealed generally good healing of the proximal stented segment. The distal stented segment showed moderate concentric restenosis with signal rich region close to the luminal surface accompanied by signal attenuation (obscuring stent struts) (i–k) with evidence of plaque rupture (arrow in j). The most-distal stented segment (i) shows high-grade eccentric restenosis with residual intraluminal thrombus (arrow in i). These appearances indicate that the stent thrombosis was attributed to in-stent plaque rupture from neoatherosclerosis.

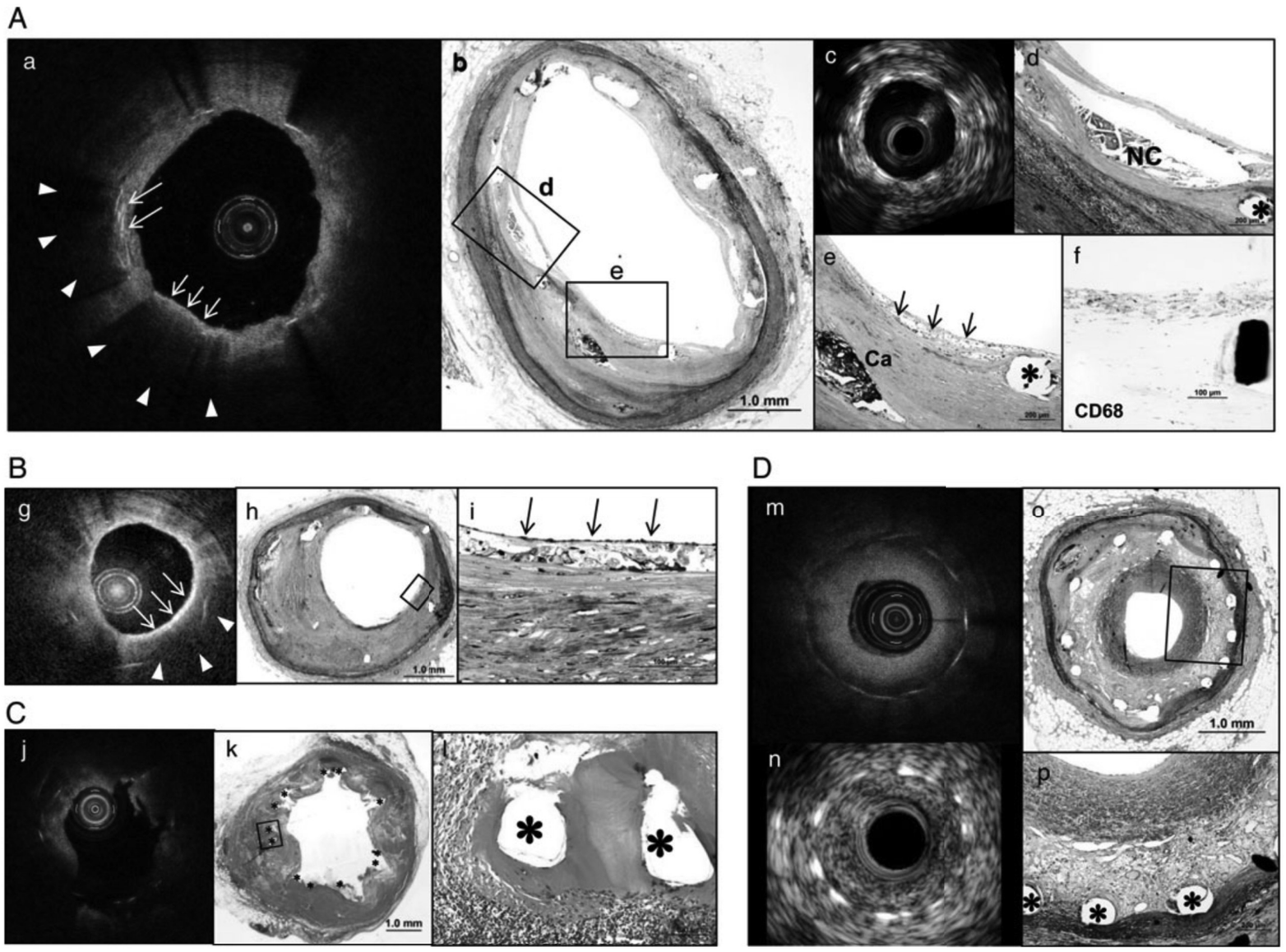
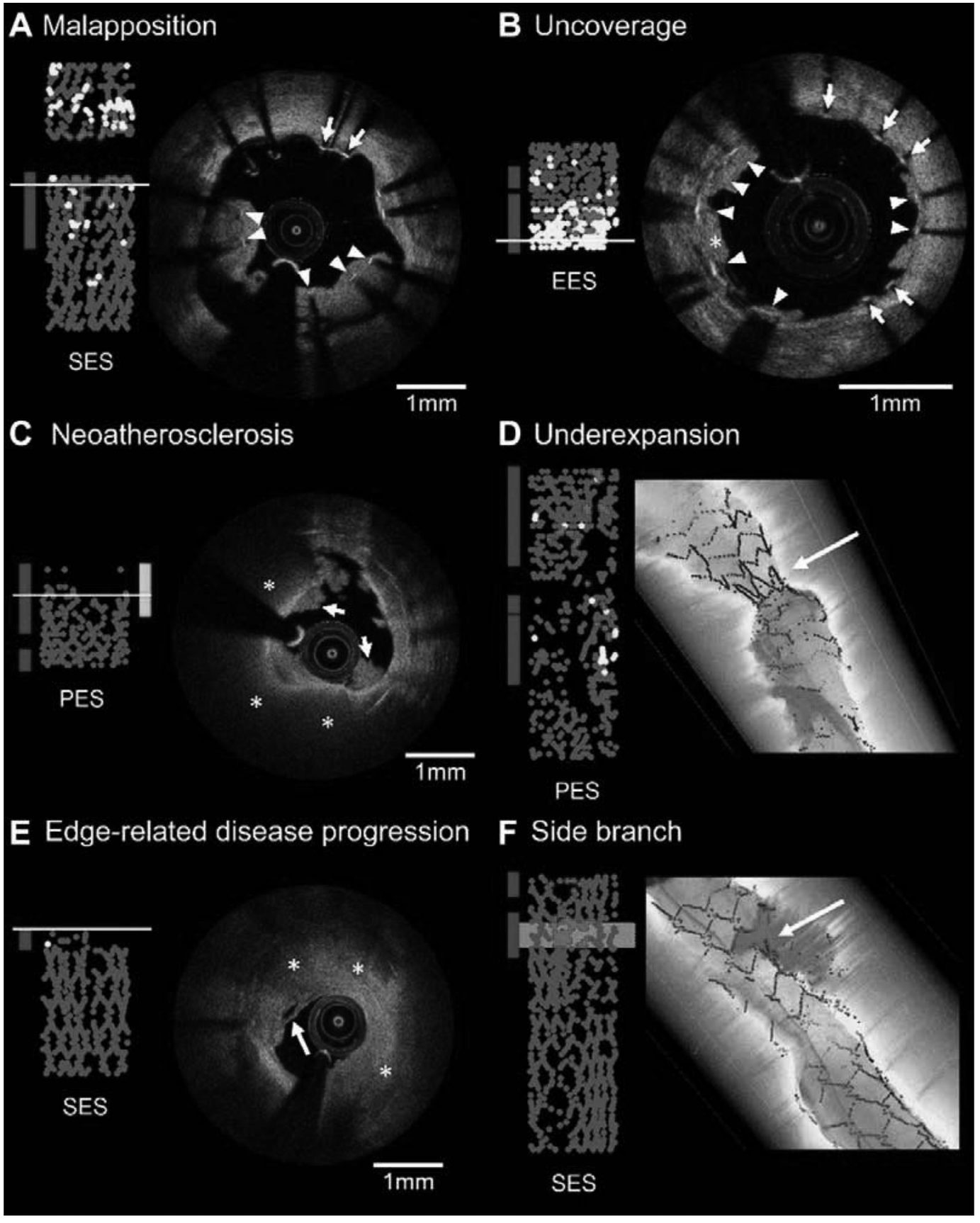


Figure 8 *Ex vivo* intravascular imaging with corresponding histologic sections showing stented coronary lesions with (*A* and *B*) and without (*C* and *D*) neoatherosclerosis. (a), (j), and (m) show optical coherence tomography images and (g) shows an optical frequency domain imaging image, while (c) and (n) show intravascular ultrasound images. (*A* and *B*) Neoatherosclerosis characterized by foamy macrophage accumulation can be detected by optical coherence tomography/optical frequency domain imaging as a thin bright signal (white arrows in [a] and [g]) with a trailing shadow (i.e. signal attenuation; white arrowheads in [a] and [g]). Linear, highly backscattering region (yellow arrows in [a]) with attenuation (white arrowheads in [a]) indicates the presence of cholesterol crystals in the necrotic core. The presence of superficial foamy macrophages (e and i) was confirmed by immunostaining using anti-CD68 antibody (f). Note the presence of fragmented calcification behind the superficial foamy macrophages in (e), which cannot be detected by optical coherence tomography in (a). (*C*) Hypersensitivity reaction in a sirolimus-eluting stent. Optical coherence tomography shows signal poor region in the deeper neointima (j) and histology demonstrated extensive inflammation predominantly consisting of eosinophils and T-lymphocytes with excessive fibrin deposition around stent struts (malapposition) (k and l). (*D*) Signal poor region without attenuation in the deeper intima as assessed by optical coherence tomography (m). The corresponding histologic images (o and p) show granulation tissue consisting of extracellular matrix and angiogenesis with varying degree of inflammatory cells. (*B*) is reproduced with permission from Ref.[51]


A Malapposition
SES
1mm
B Uncoverage
EES
1mm
C Neoatherosclerosis
PES
1mm
D Underexpansion
PES
E Edge-related disease progression
SES
1mm
F Side branch
SES

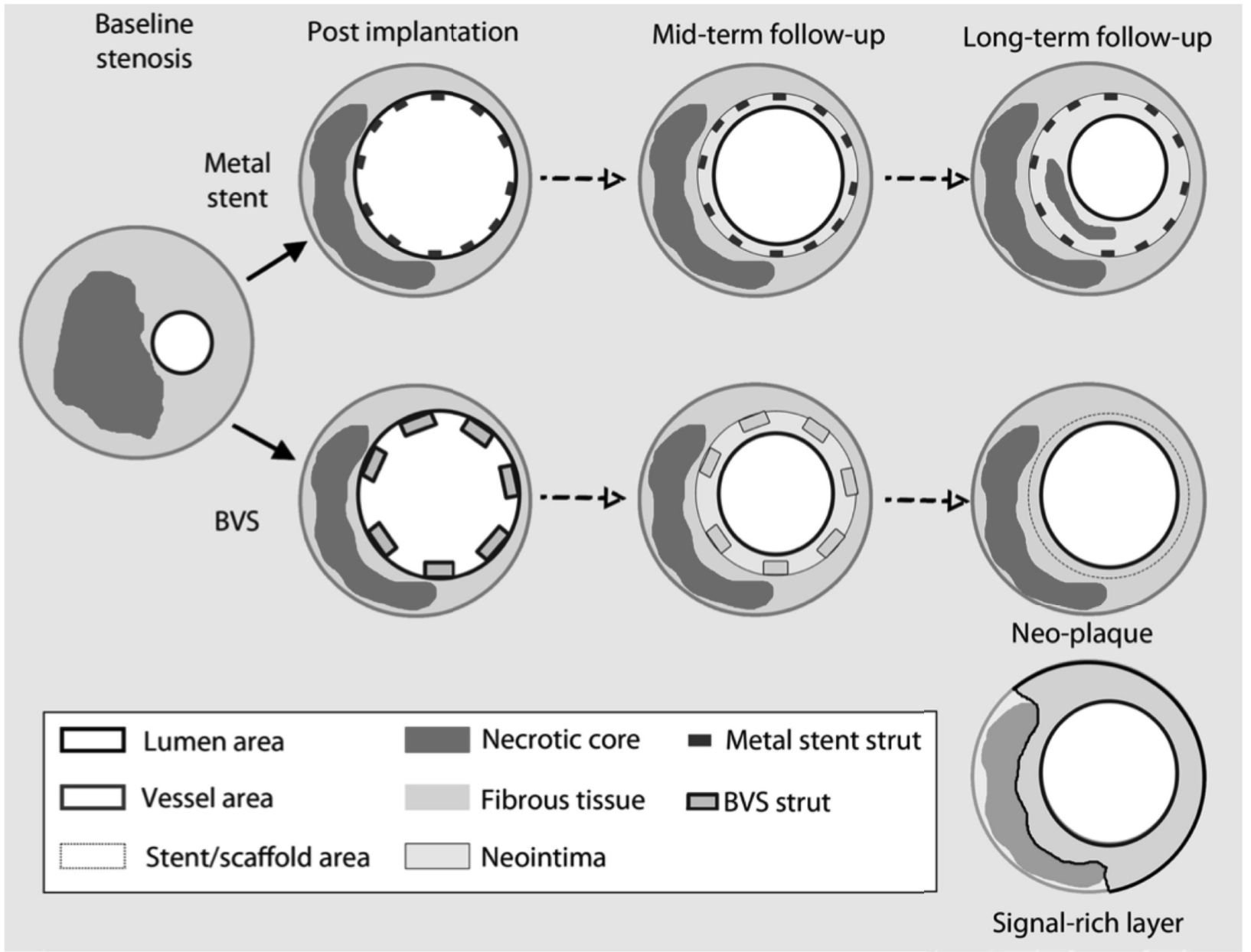


Fig. 6 ▲ Paradigm of healing response in metal stents and bioresorbable scaffolds. After metal stent implantation, struts are preserved and the neointimal area is clearly delineated between the stent and lumen contour even at long-term follow-up, with possible development of neoatherosclerosis within the neointima. Conversely, in long-term follow-up of bioresorbable scaffolds, neointimal boundaries are unclear after bioresorption (*dotted line*), and the intima resembles a native plaque, defined as neoplaque. The signal-rich layer is the layer that separates the underlying plaque components from the lumen. *BVS* bioresorbable vascular scaffold. (Adapted from Karanasos et al. [57])

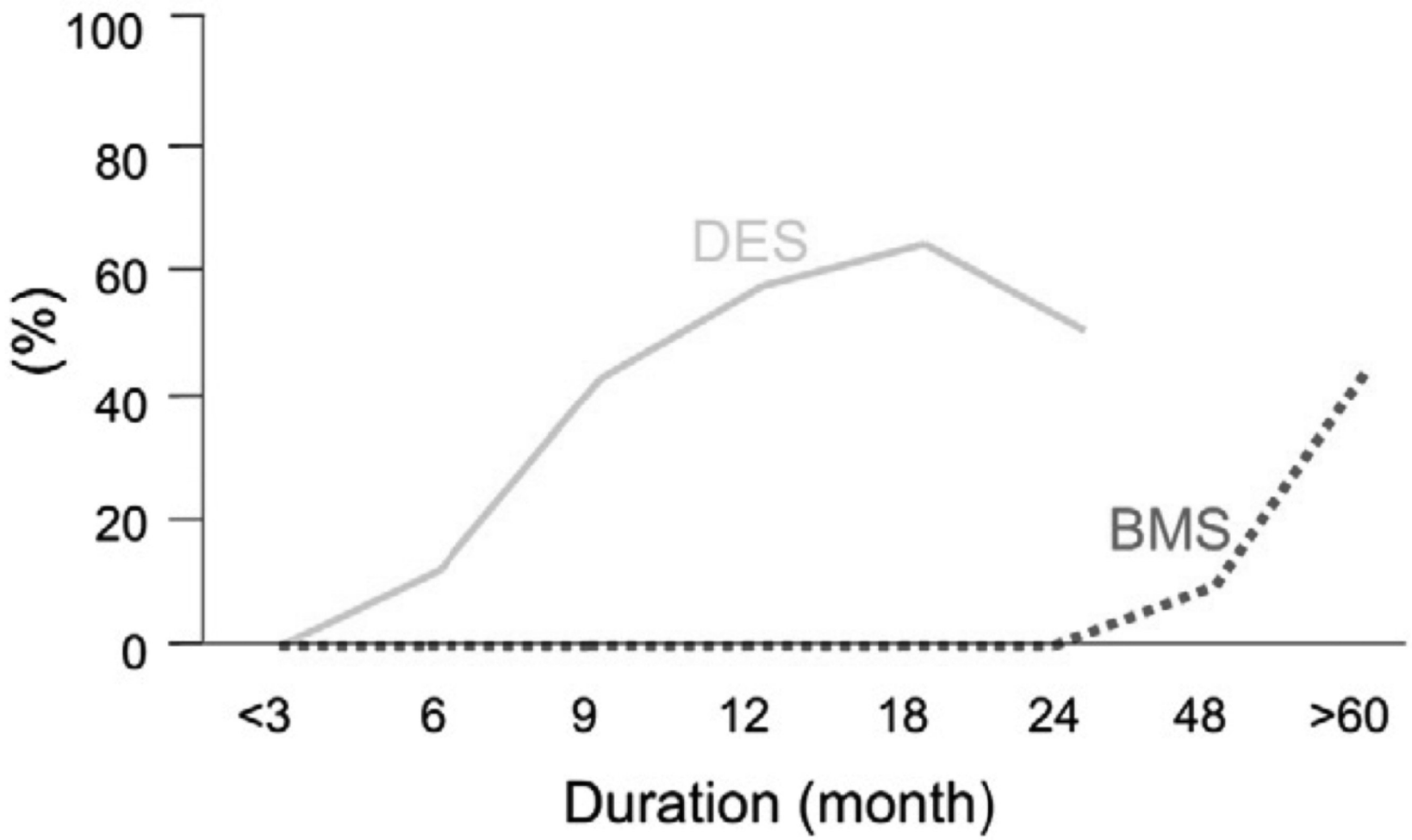


Figure 1 **Different Time Points of the Neoatherosclerosis**

Percentage of patients with atherosclerotic change in drug-eluting stent (DES) versus bare-metal stent (BMS) in relation to duration of implant at autopsy is depicted (24). Note the atherosclerotic change in sirolimus-eluting stents is seen in >40% of cases by 9 months; in the BMS, the atherosclerotic change does not begin to appear until 2 years, and remains a rare finding until 4 years.

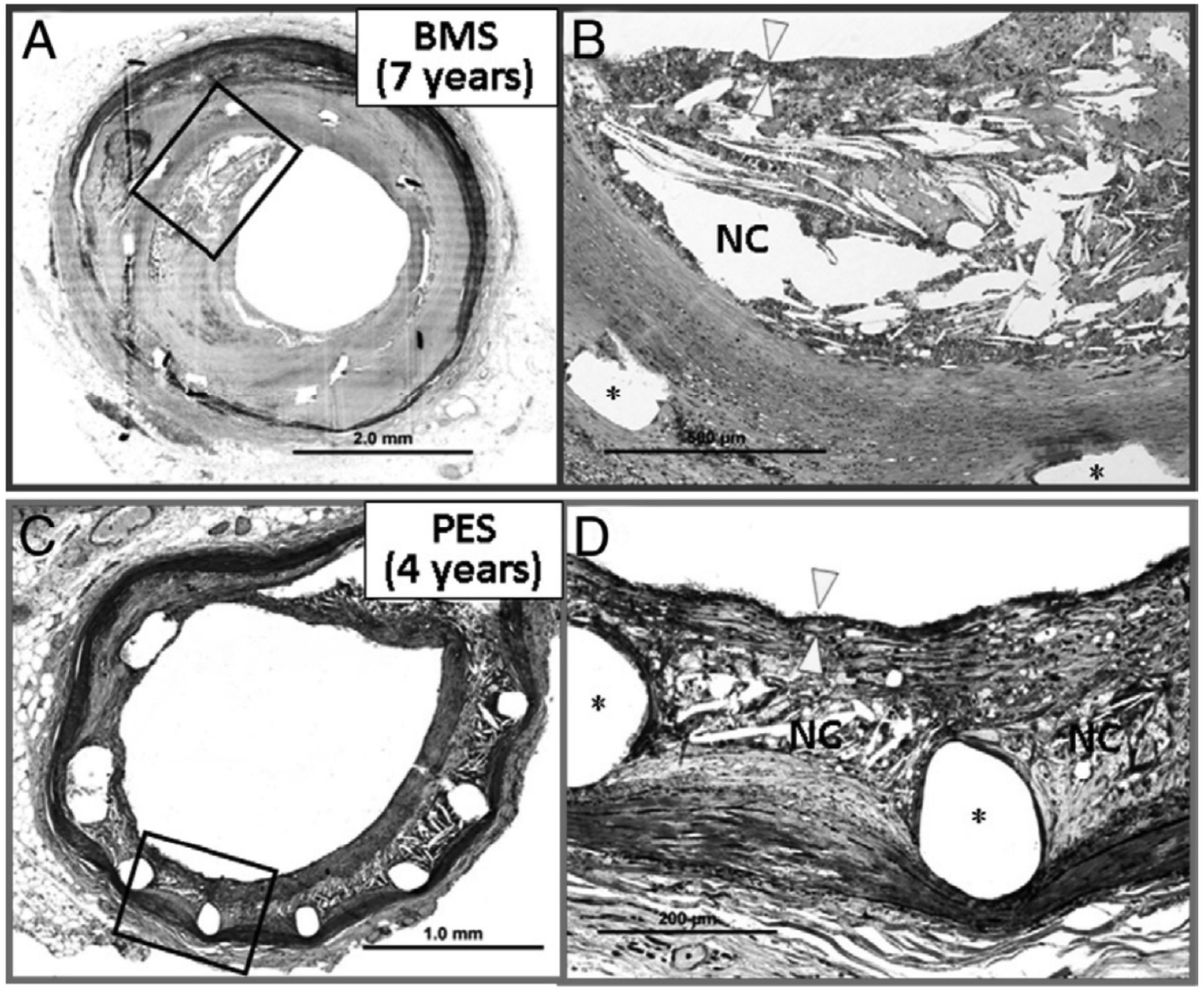


Figure 2 **Histological Findings of Neoatherosclerosis**

(A) Cross-sectional histology of bare-metal stent (BMS) implanted in the coronary artery for 7 years antemortem (Movat, ×20). **(B)** High-power image of the **box in A** (×100). A large necrotic core (NC) containing cholesterol crystals is identified within the neointima. The fibrous cap overlying the NC is infiltrated by numerous foamy macrophages and is markedly thinned (**yellow arrowheads** point to thinnest portion), which resembles vulnerable plaque encountered in native coronary arteries. The **asterisks** represent metal struts. **(C)** Cross-sectional histology of paclitaxel-eluting stent (PES) implanted in the coronary artery for 4 years antemortem (Movat, ×40). **(D)** High-power image of the **box in C** (×200). A relatively small NC containing cholesterol crystals is formed around metal struts **(asterisk)**. The fibrous cap is infiltrated by numerous foamy macrophages and is markedly thinned (**yellow arrowheads** point to thinnest portion).