

Coronary Aneurysms After Drug-Eluting Stent Implantation

Clinical, Angiographic, and Intravascular Ultrasound Findings

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- Objectives** This study sought to assess clinical, angiographic, and intravascular ultrasound (IVUS) findings in patients developing coronary aneurysms (CANs) after drug-eluting stent (DES) implantation.
- Background** The long-term safety of DES remains unsettled.
- Methods** This study analyzed 1,197 consecutive patients with late angiographic evaluation after DES implantation. In 15 patients (1.25%, 95% confidence interval: 0.58 to 1.93), CANs developed at follow-up. Analyses included quantitative angiography and volumetric IVUS.
- Results** DES developing CANs were more frequently implanted during acute myocardial infarction and were longer than those without this outcome. The elapsed time from DES implantation to CAN diagnosis was 313 ± 194 days. Angiographically, maximal CAN diameter measured 5.1 ± 1.2 mm. On IVUS, CAN external elastic lamina area was 32 ± 13.1 mm² and incomplete apposition area was 12.1 ± 8.6 mm². Two patients presented with acute myocardial infarction secondary to DES thrombosis. Four additional patients presented with unstable angina and underwent CAN aggressive dilation (3 were also treated for concomitant in-stent restenosis). Dual antiplatelet therapy was recommended in the remaining 9 patients who were asymptomatic at CAN diagnosis, but 1 of them eventually died of cardiogenic shock after a CAN-related myocardial infarction. After a mean follow-up of 399 ± 347 days, the 1-year event-free survival was $49 \pm 14\%$ and was related to CAN size on IVUS. In 2 patients, CANs disappeared at repeated late angiography and IVUS showed abluminal CAN thrombosis.
- Conclusions** After DES implantation, CANs are rare and may be detected in asymptomatic patients. However, CANs are frequently associated with adverse clinical events as a result of DES restenosis and DES thrombosis. Further studies are required to determine the implications of this distinct new entity. (J Am Coll Cardiol 2009;53:2053–60)
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The use of drug-eluting stents (DES) during coronary interventions has exploded in recent years because of their dramatic ability to inhibit neointimal proliferation (1–3). However, DES may affect the normal healing process of the vessel wall after vascular injury, resulting in delayed endothelialization (4,5), and currently, prolonged dual antiplatelet therapy is recommended in these patients (6,7). Furthermore, the pharmacological effects of DES may influence the remodeling process and lead to late incomplete stent apposition (8–11).

The appearance of angiographic coronary aneurysms (CANs) after coronary interventions is very rare (12). The

occurrence of angiographic CAN after DES has generated great interest but, to date, this finding has only been marginally reported in large-scale clinical trials or described in anecdotal case reports (13–16). Although CAN may develop as a result of exaggerated positive remodeling of the vessel wall (13–16), the underlying pathophysiology remains unknown. In some patients, this phenomenon has been linked to hypersensitivity reactions (15), bacterial arteritis (17–21), or other rare predisposing factors such as Kawasaki disease (14). Finally, it has also been suggested that DES-related CAN might predispose to DES thrombosis (15,18). Currently, however, the clinical implications of angiographic CAN remain uncertain.

The aim of the present study was to systematically assess clinical, angiographic, and intravascular ultrasound (IVUS) findings in patients developing angiographic CAN after DES implantation.

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Abbreviations
and Acronyms

CAN = coronary aneurysm
CI = confidence interval
DES = drug-eluting stent(s)
IVUS = intravascular
ultrasound

Methods

Patient selection and study design. From the clinical and angiographic databases of the Cardiovascular Institute, Clínico San Carlos University Hospital (Madrid, Spain), 1,197 consecutive patients with late angiographic evaluation after DES implanta-

tion were identified and analyzed. This represents an angiographic follow-up rate of 71% in the initial 1,685 patients treated with DES in our institution. Fifteen of these patients (1.25%) had CANs at repeated angiographic evaluation. Once the diagnosis of CAN was established, patients were prospectively surveyed according to a specific protocol. The study was an investigator-driven initiative. All patients gave written informed consent to the study protocol that was approved by the institutional ethical review board.

Follow-up and definitions. At our institution, patients undergoing DES implantation are routinely scheduled for a stress test and angiographic evaluation at 9-month follow-up or earlier if clinically indicated. Clopidogrel (75 mg/day) was maintained for 9 months. However, in asymptomatic patients with a negative exercise test result, late angiography may be halted if this is requested by the referring physician. By protocol, however, all patients with recurrent symptoms or with objective evidence of ischemia undergo late angiographic evaluation.

Continuous, prospective, clinical surveillance was indicated in all patients with the diagnosis of CAN to assess long-term outcomes. A pre-defined, structured, detailed questionnaire was used. Major events were verified against source documentation. Clinical events (death, myocardial infarction, target vessel revascularization) were adjudicated by personnel unaware of the intervention results and late angiographic findings. Myocardial infarction diagnosis required 2 of the following: 1) prolonged (>30 min) chest pain; 2) a creatine kinase increase greater than twice the upper normal value (with abnormal MB fraction); and 3) appearance of new pathological Q waves. The Academic Research Consortium definition of definitive or probable stent thrombosis was used (2). Hypersensitivity reactions were specifically sought in every patient including dermatological reactions, anaphylaxis, arthralgia, and fever. Finally, laboratory tests with complete blood cell counts (including eosinophils) and immunoglobulin E titres were performed at CAN diagnosis and at follow-up.

Angiographic analysis. Coronary angiograms (baseline, intervention, follow-up) were carefully analyzed by dedicated personnel at an angiographic core laboratory. On qualitative analysis, CAN was defined as a localized angiographic dilation of the vessel lumen (50% larger than the adjacent reference vessel) at late angiography, closely related to the underlying DES or its edges, that was not present immediately after the procedure (12). Particular attention

was taken to identify dissections or extravasation suggestive of contained perforations during the initial intervention. Quantitative coronary angiographic analysis was performed with an automatic edge-detection system (MEDIS, CMS 4.0, Leiden, the Netherlands). The angiographic analysis included the treated segment (lesion site + the treated region + the adjacent [5-mm] vessel on each side). Restenosis was defined as >50% diameter stenosis at follow-up. **IVUS.** All IVUS studies (30/40-MHz mechanical transducers) were performed using an automated pullback system (0.5 mm/s) and recorded on sVHS videotapes for subsequent off-line analysis (22,23). Incomplete DES apposition was defined as ≥ 1 stent strut clearly separated from the vessel wall, with blood speckling behind it, in a vessel segment not encompassing a side-branch exit (8-11). Quantitative IVUS analyses were performed using a previously validated automatic contour detection system (EchoScan, Tomtec, Germany) (22,23). Diameters, areas (every 0.3 mm of DES length), and volumes of lumen, stent, and external elastic lamina were measured. Subsequently, at the segment with incomplete apposition, care was taken to analyze the lumen outside the stent and the maximal depth, area, length, and volume of this lumen. The lumen outside the stent was considered to be part of the effective total vessel lumen (8-11). The extent of incomplete apposition was further evaluated by measuring the arc of malapposition and the number of nonapposed DES struts (8-11). Images suggestive of partial thrombosis of this space were analyzed. The volume of plaque behind the stent was calculated as the external elastic lamina volume minus the sum of the DES volume and the lumen outside the stent volume. On IVUS, CAN was defined as a maximal effective lumen area >50% of reference lumen area (8-11).

Statistical analysis. Data are presented as values and percentages or mean \pm SD. Categorical variables were compared with the chi-square test or the Fisher exact test. The Student *t* test was used for the comparison of continuous variables. Event-free survival was estimated by Kaplan-Meier analysis. The SPSS package version 12.0 (SPSS Inc., Chicago, Illinois) was used. A *p* value of <0.05 was considered statistically significant.

Results

Initial procedural findings. Baseline characteristics of the 15 patients in whom angiographic CANs developed (incidence 1.25%, 95% confidence interval [CI]: 0.58 to 1.93) (Fig. 1) and of the remaining 1,182 cases without CAN are presented in Table 1. Patients who develop CAN had initial procedures more frequently performed during an acute myocardial infarction and in occluded vessels, and more frequently required long DES and multiple DES and had residual dissections as compared with patients in whom CAN did not develop (Table 1). One of these patients had chronic myeloid leukemia, 1 had lung carcinoma, and another required prior surgery for bladder cancer.

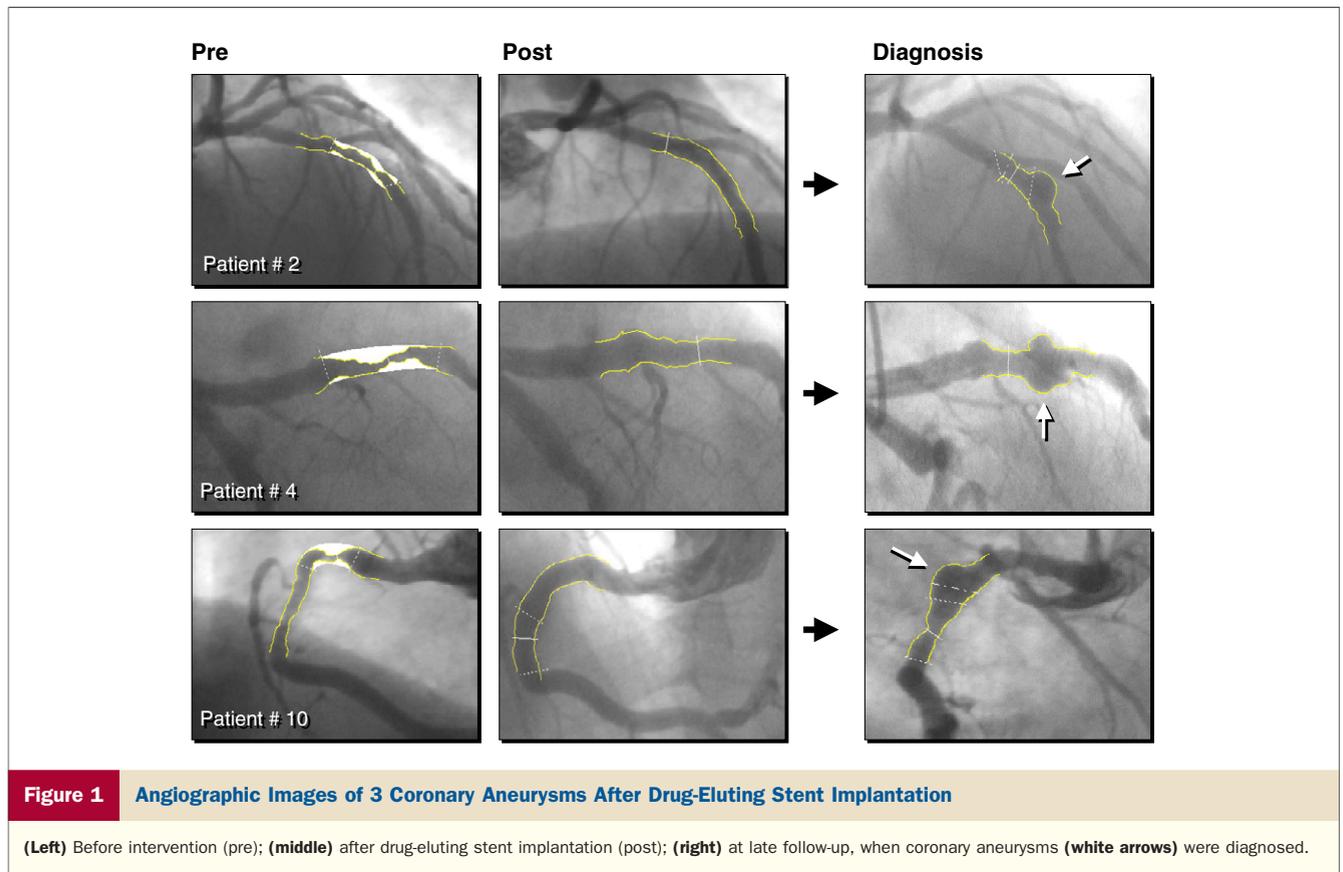


Figure 1 Angiographic Images of 3 Coronary Aneurysms After Drug-Eluting Stent Implantation

(Left) Before intervention (pre); (middle) after drug-eluting stent implantation (post); (right) at late follow-up, when coronary aneurysms (white arrows) were diagnosed.

During the initial interventions 1 CAN patient suffered from abdominal sepsis, and another, with acquired immunodeficiency syndrome that had withheld the antiretroviral therapy, presented a prolonged episode of fever of unknown etiology. Both patients eventually responded to antibiotic therapy. Two asthmatic patients suffered from bronchospasm crisis that resolved with conventional management. However, no additional patient developing CAN presented with signs of infection or allergic reaction, or had fever, leukocytosis, or hypereosinophilia during initial admission. **CAN diagnosis.** The elapsed time from DES implantation to CAN diagnosis was 313 ± 194 days. Two patients with CANs presented with large acute myocardial infarctions as a result of DES thrombosis (633 and 727 days after DES implantation, both on aspirin alone). In the first patient, primary angioplasty required the use of aggressive balloon dilation of the proximal CAN to obtain angiographic success. However, this patient had an advanced lung carcinoma and died suddenly (without chest pain or electrocardiographic changes) 48 h later. Autopsy examination could not be obtained. In the second, angiographic evidence of DES thrombosis was obtained 24 h after the infarction, and during an elective repeated intervention, residual angiographic CAN persisted (although reduced in size) despite aggressive balloon dilation and additional DES implantation.

Four additional patients presented with unstable angina at the time of CAN diagnosis. Three of them, with CANs located in the proximal part of the DES, also had concomitant severe distal-edge in-stent restenosis. In these 3 patients the distal DES restenosis was treated with repeated DES implantation, whereas the proximal CAN underwent aggressive balloon angioplasty in an attempt to appose the stent to the vessel wall. The fourth patient presented with a CAN on the left anterior descending coronary artery but had no significant stenosis. A CAN-related distal embolization was suspected because of recurrent angina associated with troponin elevation and negative T waves on the anterior leads, and eventually aggressive CAN balloon angioplasty was successfully performed. In these 6 patients with CANs requiring reintervention, larger balloon diameters (3.75 ± 0.5 mm vs. 3.0 ± 0.5 mm, $p < 0.05$) were used as compared with those used at initial DES implantation.

The remaining 9 patients were asymptomatic and had negative exercise test results at CAN diagnosis. In all of these cases, CANs were incidental findings detected in a scheduled routine angiographic evaluation and lifelong dual antiplatelet therapy was recommended. After 445 ± 345 days of follow-up, 8 patients remained asymptomatic and event free. However, 1 patient withheld clopidogrel therapy and died (243 days after diagnosis) of cardiogenic shock secondary to a CAN-related large acute anterior myocardial infarction, probably as a result of DES thrombosis (Table 2). Figure 2 shows the clinical

Table 1 Baseline Clinical, Angiographic, and Procedural Characteristics at the Time of Initial DES Implantation

	CAN (n = 15)	No CAN (n = 1,182)	p Value
Age (yrs)	58 ± 11	63 ± 11	0.85
Female sex	3 (20)	278 (23)	1.00
Risk factors			
Diabetes mellitus	6 (40)	487 (41)	0.92
Hyperlipidemia	9 (60)	726 (61)	0.91
Hypertension	11 (73)	729 (63)	0.39
Ever smoked	12 (80)	733 (62)	0.15
Clinical features			
AMI	6 (40)	179 (15)	0.02
Unstable angina	4 (26)	631 (53)	
Stable angina	5 (34)	372 (32)	
Previous myocardial infarction	3 (20)	492 (42)	0.09
Ejection fraction (%)	57 ± 11	64 ± 13	0.19
Angiographic data, lesions			
LAD	11 (73)	764 (49)	0.27
LCX	2 (13)	293 (19)	
RCA	2 (13)	434 (28)	
Total occlusion	4 (27)	192 (12)	0.10
B2C lesion	8 (57)	1,114 (71)	0.25
Procedural characteristics			
DES type (SES/PES/other)	5/10/0	637/768/160	0.26
DES length (mm)	26.8 ± 11	20.8 ± 10	0.02
Multiple DES (%)	4 (27)	139 (9)	0.04
Maximal pressure (atm)	16.4 ± 2.4	16.1 ± 2.8	0.68
Maximal balloon diameter (mm)	3.1 ± 0.5	3.0 ± 0.4	0.55
Residual dissection (%)	4 (27)	47 (3)	0.001
Reference vessel (mm)	2.75 ± 0.5	—	
Balloon/artery ratio	1.13 ± 0.1	—	

Values are mean ± SD or n (%).
— = not available; AMI = acute myocardial infarction; CAN = coronary aneurysm; DES = drug-eluting stent(s); LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; PES = paclitaxel-eluting stent(s); RCA = right coronary artery; SES = sirolimus-eluting stent(s).

outcome (mean follow-up 399 ± 347 days) for the entire series of patients.

At the time of CAN diagnosis and at late clinical follow-up, no patient presented with fever, signs of infection, or allergic reactions. Except for the patient with chronic myeloid leukemia, none of them had leukocytosis (leukocytes 9.430 ± 3.600/μl; 64 ± 18% neutrophils), hypereosinophilia (1.45 ± 1.28%), or abnormal immunoglobulin E titres (37 ± 21 IU/ml) during the study period. **Angiographic and IVUS findings.** Angiographic data before and after initial DES implantation and at the time of CAN diagnosis are presented in Tables 1 and 2. Angiographically, the mean maximal CAN diameter was 5.1 ± 1.2 mm. Five CANs were located in the proximal third and 10 in the mid DES segment (including 4 patients with overlapping DES). Angiographically, 10 CANs were classified as saccular, 1 as fusiform, and 4 as complex/multilobulated.

IVUS studies were obtained in 13 patients (Fig. 3). All angiographic CANs also fulfilled the IVUS definition of aneurysm. In all cases, IVUS readily detected malapposition

Table 2 Clinical, Angiographic, and Intravascular Ultrasound Findings in Patients With CANs

Patient #	Age (yrs)/Sex	DES Type	Vessel/Initial Symptoms	Pre-DES QCA MLD/%DS	Post-DES QCA MLD/%DS	Time (Days) to Angiographic Diagnosis	CAN Clinical Presentation	CAN Size QCA (mm)	IVUS ISA Area/Volume (mm ² /mm ³)	Intervention CAN/ISR	Follow-Up (Days)
1	56/M	Taxus	LAD/UA	1.12/65	2.0/20	279	Asymptomatic	4.73	19.7/96.2	No	958
2	53/M	Taxus	LAD/SA	0.73/75	2.84/15	212	Asymptomatic	5.32	20.7/92.2	No	952
3	65/M	Taxus	LAD/UA	0.79/70	1.89/15	38	UA	3.43	1.8/38.5	BA/No	955
4	61/M	Taxus	LAD/AMI	0.67/80	2.24/15	184	Asymptomatic	8.1	NA/NA	No	733
5	75/F	Taxus	LAD/AMI	0.0/100	2.79/25	269	Asymptomatic	5.16	33.5/256.4	No	243 (died)
6	55/M	Cypher	LAD/UA	0.98/60	1.93/14	727	AMI	4.45	11.1/87.8	BA/DES	818
7	60/M	Cypher	LAD/SA	1.19/60	2.35/15	633	AMI	3.78	14.9/160.5	BA/DES	1 (died)
8	59/M	Taxus	LAD/AMI	0.0/100	2.22/11	188	Asymptomatic	4.75	NA/NA	No	401
9	41/M	Taxus	LAD/AMI	NA/NA	NA/NA	631	Asymptomatic	5.33	9.4/50.7	No	394
10	63/M	Taxus	RCA/SA	1.14/70	3.29/9	246	SA	7.29	10.2/54.6	BA/DES	380
11	49/M	Taxus	LAD/SA	1.03/75	3.19/8	275	Asymptomatic	6.23	5.7/18.9	No	221
12	75/F	Cypher	LAD/AMI	1.27/55	2.12/8	276	Asymptomatic	4.90	13.9/78.3	BA/DES	222
13	61/M	Cypher	RCA/UA	0.0/100	2.58/13	183	UA	4.74	7.7/24.7	BA/DES	256
14	32/F	Cypher	LCX/SA	1.33/60	2.36/13	307	SA	3.86	4.1/6.1	No	87
15	60/M	Taxus	LCX/AMI	0.0/100	2.41/20	246	Asymptomatic	4.29	4.9/26.5	No	54

BA = balloon angioplasty; DS = diameter stenosis; ISR = in-stent restenosis; IVUS ISA = intravascular ultrasound-detected incomplete stent apposition; MLD = minimal lumen diameter; NA = not available; QCA = quantitative coronary angiography; SA = stable angina; UA = unstable angina; other abbreviations as in Table 1.

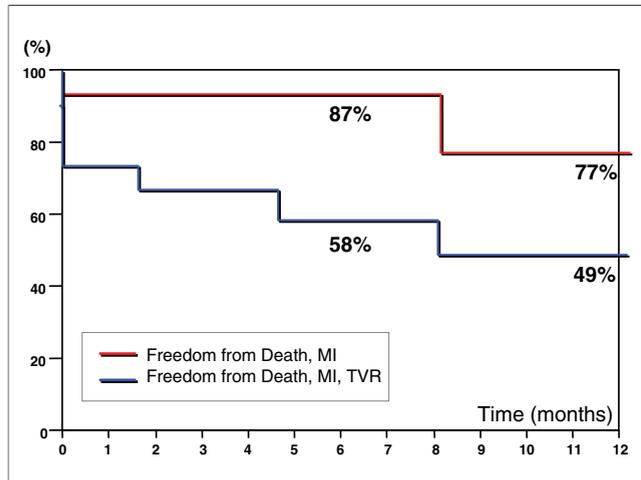


Figure 2 Event-Free Survival Estimates After the Diagnosis of Coronary Aneurysms

At 1 year, freedom from death or myocardial infarction (MI) was $77 \pm 12\%$ (95% confidence interval: 54% to 100%) and freedom from death, MI or target vessel revascularization (TVR) was $49 \pm 14\%$ (95% confidence interval: 22% to 76%).

with a prominent distance between the DES struts and the vessel wall. The extent of incomplete apposition (length, mean and maximal area, and volume) and other relevant IVUS features are summarized in Table 3. In the 6 patients who underwent repeated interventions, maximal area of

incomplete apposition ($11.6 \pm 3 \text{ mm}^2$ vs. $5.5 \pm 0.6 \text{ mm}^2$, $p < 0.05$) was significantly reduced after treatment.

Angiographically, CAN size was similar in the 3 patients suffering DES thrombosis as compared with patients without this event. On IVUS, however, patients with DES thrombosis had significantly larger CANs as compared with patients without DES thrombosis (Table 4). Further, event-free survival was also better in patients with smaller CANs on IVUS (Table 4). During additional follow-up, spontaneous abluminal CAN thrombosis was suspected on repeated angiography and confirmed with IVUS in 2 patients.

Discussion

The main findings of our study are as follows: 1) CANs are rarely detected (1.25%) after DES implantation; 2) coronary angiography is able to provide an accurate diagnosis of this entity; 3) IVUS provides further anatomic insights, including the extent of DES malapposition, which seems to have major prognostic implications; 4) CAN may be detected in asymptomatic patients who have good long-term clinical outcome on an indefinite dual antiplatelet regimen; 5) however, CAN may be associated with DES restenosis, and different repeated interventions are required to address these distinct entities; and 6) CAN may also present as DES thrombosis.

Major attention recently has been focused on late complications after DES implantation (8–21). The present

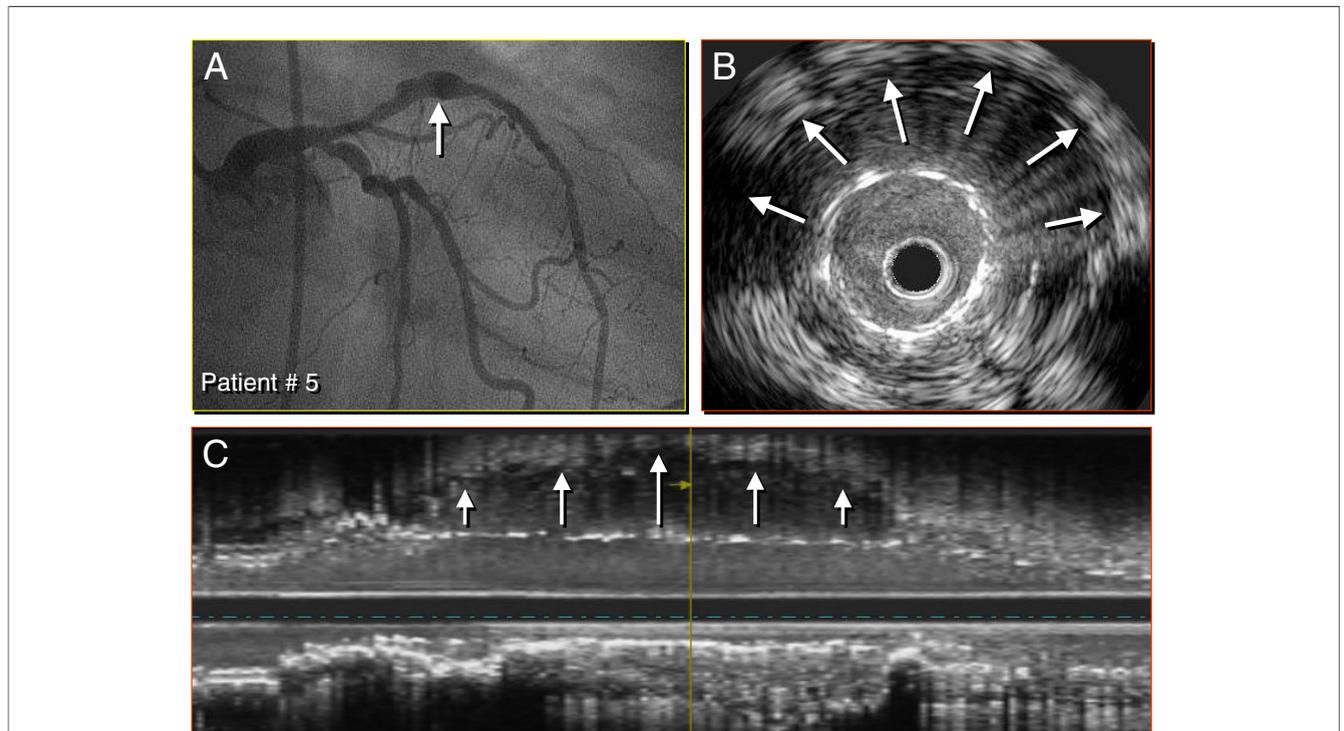


Figure 3 Intravascular Ultrasound Images of a Coronary Aneurysm

(A) Angiographic image of a coronary aneurysm in the left anterior descending coronary artery (arrow). (B) Intravascular ultrasound image showing the aneurysm with severe incomplete apposition of the stent struts (arrows). (C) Longitudinal reconstruction of the vessel disclosing the aneurysm and the full extent of malapposition (arrows).

Parameter	Value
EEL mean area (mm ²)	26.7 ± 9.7
EEL maximal area (mm ²)	32.0 ± 13.1
EEL volume (mm ³)	303.7 ± 194.9
DES mean area (mm ²)	7.6 ± 2.0
DES minimal area (mm ²)	6.6 ± 1.8
DES maximal area (mm ²)	8.8 ± 2.4
DES volume (mm ³)	70.6 ± 42.6
Plaque behind DES mean area (mm ²)	12.8 ± 5.8
Plaque behind DES maximal area (mm ²)	17.5 ± 8.1
Plaque behind DES volume (mm ³)	169.9 ± 144.8
ISA mean area (mm ²)	7.0 ± 4.8
ISA maximal area (mm ²)	12.1 ± 8.6
ISA volume (mm ³)	76.2 ± 68.4
Effective (total) maximal lumen area (mm ²)	19.8 ± 9.6
Effective (total) lumen volume (mm ³)	135.1 ± 97.9
ISA maximal depth (mm) (strut-CAN wall)	2.2 ± 0.8
Number of struts with ISA	4.5 ± 1.3
ISA maximal arc (angle °)	135 ± 59
ISA length (mm)	9.2 ± 4.2
ISA partial thrombosis	3

EEL = external elastic lamina; ISA = incomplete stent apposition; other abbreviations as in Table 1.

report represents the first systematic study to provide a comprehensive assessment of patients in whom angiographic CAN develops after DES implantation. Previous studies have only reported anecdotal descriptions of angiographic CAN after DES, either from large-scale clinical trials or as case-report descriptions (12–16). In these scarce reports, outcome has ranged from asymptomatic patients, with CAN representing just an incidental angiographic finding without clinical consequences, to CAN associated with DES thrombosis (15,18). In the TAXUS VI trial (24), involving long and complex lesions, in 1.4% of patients in the paclitaxel-eluting stent arm late acquired aneurysms developed (vs. 0.5% in the bare-metal stent group, p = 0.62) but no additional information was provided on these patients. In a recent letter to the editor, Bavry et al. (16) described preliminary findings of 4 patients with angiographic CANs after DES implantation. Two patients were managed conservatively and, on continued clinical surveillance, 1 evolved to CAN resolution. Two patients had successful intervention: 1 with percutaneous coiling and 1 by surgical excision and coronary bypass grafting; interestingly enough, pathological examination in the latter patient showed eosinophilic infiltration of the vessel wall (16).

Although the underlying mechanism for CAN development remains unknown, several hypotheses may be postulated. Extensive acute vessel damage during the initial procedure, hypersensitivity reactions, infectious processes, and phenomena resembling extreme cases of late acquired malapposition may all be implicated.

Acute deep vessel wall injury. Early CAN development may be a consequence of mechanical problems resulting from complicated procedures, large dissections, contained perforations, or even vessel ruptures (12). In these patients, *pseudo-*

aneurysms may actually develop rather than true CANs, and this rare substrate has been previously shown after various coronary interventions (12). Notably, acute eosinophilic infiltrates at the vessel wall have been identified in patients suffering from coronary dissections (17). In this complicated setting, DES implantation might impair the normal healing process of the vessel wall (25,26), favoring CAN development. Interestingly, systemic anti-inflammatory agents also seem to predispose to CAN formation (27). In our series, procedural-related major dissections were detected in 5 patients (4 patients had residual dissections after the procedure). Further, total vessel occlusion, which may also predispose to wall disruption as a result of subintimal wire advancement, was present in 4 cases. However, particularly aggressive interventions (pressures or balloon to artery ratios) were not identified in our patients. Finally, the potential influence of concurrent neoplasia or acquired immunodeficiency syndrome, on vessel wall healing, remains to be defined.

Hypersensitivity reactions. Virmani et al. (15) demonstrated localized hypersensitivity vasculitis, with accumulation of T-lymphocytes and intense eosinophilia, in a patient who eventually died of late DES thrombosis. Lack of endothelial coverage and severe DES malapposition caused by aneurysmal vessel enlargement was shown. Hypersensitivity reaction was thought to be caused by the polymer (16). Likewise, high-intensity uptake of gallium localized at the site of previously implanted DES also has been reported (28).

Alternatively, a *generalized* hypersensitivity reaction has been suggested in some patients suffering from DES thrombosis. The RADAR (Research on Adverse Drug events And Reports) study (29) showed 17 distinct cases of hypersensitivity or systemic allergic reactions “probably or certainly” related to the DES. Clinical manifestations were primarily cutaneous and usually begun within 2 weeks of DES implantation. Notably, 4 of these patients presented DES thrombosis, and autopsy studies confirmed intra-DES eosinophilic inflammation and lack of intimal healing. No patient in our series, however, had documented hypersensitivity reactions after the procedure.

Clinical Outcome	Event	No Event	p Value
DES thrombosis*	n = 3	n = 10	
Angiographic CAN diameter (mm)	4.5 ± 0.7	5.2 ± 1.3	0.36
IVUS EEL volume (mm ³)	504.5 ± 145	243.4 ± 168.9	0.035
IVUS ISA volume (mm ³)	168.2 ± 84.6	48.6 ± 31.5	0.002
IVUS effective lumen volume (mm ³)	271.8 ± 104.4	94.1 ± 47.7	0.001
Any event†	n = 7	n = 6	
Angiographic CAN diameter (mm)	4.8 ± 1.2	5.3 ± 1.2	0.48
IVUS EEL volume (mm ³)	405.3 ± 201.3	184.9 ± 105.8	0.035
IVUS ISA volume (mm ³)	100.1 ± 81.9	48.4 ± 38.3	0.18
IVUS effective lumen volume (mm ³)	167.3 ± 116.1	97.7 ± 60.9	0.21

*Definitive or probable thrombosis according to the Academic Research Consortium definition.
†Events include death, myocardial infarction, and target vessel revascularization.
EEL = external elastic lamina; ISA = incomplete stent apposition; IVUS = intravascular ultrasound; other abbreviations as in Table 1.

In-stent restenosis has also been associated with allergies to metals such as nickel, molybdenum, and chromium (15), but the potential relationship between allergies to metals and CAN formation or stent thrombosis has not been confirmed. In 4 patients of the present series both CAN and in-stent restenosis concomitantly developed, although at separate DES locations.

Focal infection. Some investigators have reported the exceedingly rare occurrence of mycotic CANs or coronary pseudoaneurysms after DES implantation (17–21). It has been suggested that local DES infection may result from direct contamination of the device at the time of delivery or from subsequent bacteremia. DES might constitute a potentially predisposing factor by blunting the local inflammatory response of the vessel wall, favoring the maintenance or extension of the infection (17). The immunosuppressive activity of DES could be implicated. In most cases *Staphylococcus aureus* infections have been shown (17–21). These patients typically present with fever and systemic manifestations, including septicemia, and a clinical picture of fulminant infection with poor prognosis. In our series, 2 patients suffered infectious processes with subsequent sepsis during initial DES procedures but (apparently) responded well to antibiotics with complete initial resolution.

Vessel remodeling and DES malapposition. This phenomenon seems to be more frequent after DES than after bare-metal stent implantation (7–11). Predictors of late-acquired malapposition include DES implantation in acute coronary syndromes, long lesions, and chronic occlusions (8,10). The MISSION study (30) suggested that after primary angioplasty, late malapposition may be recognized in up to 37% of patients treated with DES. Interestingly, in 6 of our patients (40%) DES were initially implanted during an acute myocardial infarction. In our series, CANs were also more frequently detected after long and multiple DES implantations. Finally, 4 CANs emerged from areas of DES overlap. This may suggest that, in some patients, CAN could be related to excessive vessel remodeling as a result of high drug concentrations. The appearance of angiographic CAN has been noticed in anecdotal patients serially followed up for IVUS-detected incomplete DES apposition (7–10). It could be speculated that vessel dilation may beg for further vessel dilation, and eventually, angiographically visible CAN formation. In addition, it has been suggested that late malapposition might provide a nidus for thrombus formation (23). Despite its worrisome appearance, most studies suggest that late malapposition represents a pure IVUS finding without clinical repercussions (8–11). Nevertheless, recent reports (31,32) suggested that incomplete apposition may indeed constitute a risk factor for late DES thrombosis.

Clinical implications. Currently, the natural history and the therapy of choice for patients in whom CAN develops remains unknown. Furthermore, it is still unclear whether DES are more prone to develop this complication than bare-metal stents (24). Our findings indicate that CAN may represent just incidental angiographic findings in asymp-

tomatic patients. In these cases, a continuous clinical surveillance under prolonged dual antiplatelet therapy might be indicated, providing compliance is guaranteed. This strategy is further supported by the possibility of CAN spontaneous resolution (16), as confirmed in 2 patients in the present study. Longer periods of follow-up are required to fully dissipate risk concerns in asymptomatic patients receiving a correct dual antiplatelet regimen.

However, our findings underscore that CAN may also lead to serious, potentially life-threatening clinical problems, including DES thrombosis and death. In our series, this was always related to discontinuation of dual antiplatelet therapy. Of interest, our findings also suggest that in patients with CAN, IVUS may be useful to identify those at higher risk. Patients with larger total vessel areas and larger areas of malapposition had poorer prognosis. Therefore, the fate of CAN seems to depend on its size, and in this regard, IVUS appears to be superior to angiography. Overall, the natural history of our patients was poor, suggesting that aggressive strategies should be contemplated, especially in patients with large CAN.

Lack of neointimal coverage of DES struts, severe malapposition, and rheologic factors may be implicated in the risk of CAN thrombosis. In these cases an aggressive approach (balloon overdistension, coiling, covered stents, or surgical excision) (16) seem justified to prevent this devastating complication. Currently, the challenge remains to differentiate high-risk CANs versus those associated with a benign outcome. In fact, abluminal CAN thrombosis may constitute a double-edged sword leading to complete CAN resolution in some patients but increasing the risk of DES thrombosis in others. Serial studies are required to provide mechanistic underpinnings for CAN development and related complications.

Study limitations. First, our series, despite including the largest number of patients reported to date, remains very small. Therefore, caution is required when analyzing potential predictors of this rare complication, and especially, predictors of adverse clinical events. In this regard, our findings should be just considered hypothesis generating and should be confirmed in larger series of patients. Second, despite our systematic attempt to obtain routine late angiography in this real-world patient population, eventually this information was not obtained in all patients, and this might affect our incidence estimates. Third, a control group of patients systematically followed up after bare-metal stent implantation (to compare incidence and implications of CAN) would have been of interest.

Conclusions

Development of CAN after DES implantation is rare. This unique phenomenon is usually detected in asymptomatic patients and has a benign clinical course under a dual-antiplatelet regimen. However, angiographic CAN may be associated with DES restenosis, and more importantly, with DES thrombosis. Intravascular ultrasound seems to be

useful for identifying patients at higher risk for complications. Additional studies are required to identify patients at risk for adverse events and also to determine the most reasonable intervention for this challenging new entity.

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