

Aneurysmal Degeneration of Fluoropolymer-Coated Paclitaxel-Eluting Stent in the Superficial Femoral Artery. A Rising Concern

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Abstract

Background: Although several clinical reports demonstrated a durable patency rate after a novel fluoropolymer-coated paclitaxel-eluting stent (Eluvia™; Boston Scientific, Marlborough, MA, USA) implantation, aneurysmal degeneration after implanting Eluvia™ has raised clinical concerns. Here, we report a case with exacerbated aneurysmal degeneration on serial angiography and intravascular ultrasound 50 months after Eluvia™ implantation for a superficial femoral artery lesion.

Case presentation: A 79-year-old woman with claudication in the right lower extremity decreasing her quality of life was referred to our hospital. Pre-procedural angiography showed severe stenosis from the middle-to-distal part of the right superficial femoral artery, and Eluvia™ was implanted with optimal expansion. However, the patient had a recurrence of intermittent claudication in the right lower extremity 25 months thereafter. Angiography revealed de novo stenosis in the distal part of the popliteal artery and proximal stent edge restenosis at the Eluvia™ implantation site. Subsequently, the patient underwent endovascular therapy for these lesions. In addition, intravascular ultrasound at the time of endovascular therapy revealed vessel enlargement with a mean vessel diameter of 7.2-9.9 mm at the distal edge of the Eluvia™ implantation site. However, intermittent claudication on the right side recurred again 50 months after Eluvia™ implantation. Angiography demonstrated de novo severe stenosis from the distal part of the superficial femoral artery to the middle part of the popliteal artery. Furthermore, peri-stent contrast staining was found at the distal part of the Eluvia™ implantation site. Intravascular ultrasound showed a further enlargement of mean vessel diameter to 11.9 mm at the distal edge of the Eluvia™ stent. Moreover, enlargement of the lumen and stent malapposition were also found, suggesting exacerbated aneurysmal degeneration 50 months after Eluvia™ implantation.

Conclusions: We report a case with exacerbated aneurysmal degeneration on serial angiography and intravascular ultrasound 50 months after Eluvia™ implantation for an SFA lesion. Long-term follow-up should be mandatory for patients receiving Eluvia™ implants.

Background

With the development of anti-restenotic devices, endovascular therapy (EVT) has become the first-line treatment for femoropopliteal lesions. The IMPERIAL randomized trial compared a novel fluoropolymer-coated paclitaxel-eluting stent (Eluvia™; Boston Scientific, Marlborough, MA, USA) with a polymer-free paclitaxel-coated stent (Zilver PTX™; Cook Corporation, Bloomington, IN, USA), demonstrating a durable patency rate after Eluvia™ implantation [4, 5]. However, the problem of aneurysmal degeneration after Eluvia™ implantation has been raised as a clinical issue in several reports [4-6]. Here, we report a case with exacerbated aneurysmal degeneration on serial angiography and intravascular ultrasound 50 months after Eluvia™ implantation for a superficial femoral artery (SFA) lesion.

Case Presentation

A 79-year old woman with claudication in the right lower extremity which decreased her quality of life was referred to our hospital. Past medical history included hypertension, dyslipidemia and coronary artery disease. The ankle brachial index (ABI) on the right side was 0.71. Pre-procedural angiography showed severe stenosis from the middle-to-distal part of the right SFA and an Eluvia™ drug-eluting stent (DES) (7.0 × 150 mm) was implanted with optimal expansion (Figure 1A, 1B). After stent implantation, the ABI increased from 0.71 to 0.85 and the patient's symptoms improved. Since then, she has been taking dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day). However, she had a recurrence of intermittent claudication in the right lower extremity 25 months after Eluvia™ implantation. Angiography revealed de novo stenosis in the distal part of the popliteal artery and proximal stent edge restenosis at the Eluvia™ implantation site (Figure 1C). Subsequently, the patient underwent endovascular therapy (EVT) with plain balloon angioplasty for severe stenosis in the distal part of the popliteal artery and a Zilver PTX™ (7.0 × 120 mm) was implanted for the proximal edge restenosis of the Eluvia™ stent. A completion angiogram showed an optimal angiographic result. In addition, intravascular ultrasound (IVUS, AltaView™; Terumo, Tokyo, Japan) at the time of EVT revealed vessel enlargement with a mean vessel diameter of 7.2-9.9 mm at the distal edge of the Eluvia™ implantation site (Figure 2a-2f). Thereafter, the patient was symptom-free until intermittent claudication on the right side recurred 50 months after Eluvia™ implantation. Angiography demonstrated de novo severe stenosis from the distal part of the SFA to the middle part of the popliteal artery. The popliteal artery lesion was dilated using a drug-coated balloon (INPACT Admiral™, 4.0 × 80 mm, Medtronic plc., Santa Rosa, CA, USA) and the distal SFA lesion was dilated using a drug-coated balloon (INPACT Admiral™, 6.0 × 120 mm), resulting in an adequate angiographic result. However, peri-stent contrast staining (PSS) was found by angiography at the distal part of the Eluvia™ implantation site (Figure 1D). IVUS showed a further enlargement of mean vessel diameter to 11.9 mm at the distal edge of the Eluvia™ stent (Figure 2g-2i). Moreover, an enlargement of the lumen and stent malapposition were also found, suggesting exacerbated aneurysmal degeneration 50 months after Eluvia™ implantation.

Discussion

Here, we report a patient with exacerbated aneurysmal degeneration assessed by serial angiography and IVUS 50 months after Eluvia™ implantation for an SFA lesion. Although several clinical studies reported instances of aneurysmal degeneration 12 or 24 months after Eluvia™ implantation [4-6], there have been no reports of complications with exacerbated aneurysmal degeneration assessed by serial imaging device beyond 24 months after implantation. To the best of our knowledge, this is the first report showing worsening of aneurysmal degeneration assessed by serial angiography and intravascular ultrasound 50 months after Eluvia™ implantation.

In coronary arteries, peri-stent contrast staining (PSS), that is defined as contrast staining outside the stent contour extending to $\geq 20\%$ of the stent diameter after DES implantation, is rare and has a reported incidence ranging from 1.9% to 2.2% [7, 8]. PSS could be regarded as representing an abnormal response of the vessel wall caused by DES. Several mechanisms have been proposed to account for the

development of PSS, including delayed re-endothelialization, inflammatory changes in the medial wall, and hypersensitivity reactions to drugs and polymers [9-11].

Although the 12-month duplex ultrasound examination in the IMPERIAL randomized trial reported aneurysmal degeneration in only 1.9% (6/309) of patients after Eluvia™ DES implantation [4], this rose to 8.1% (8/62) in the 12-month results of the Munster registry, thus inconsistent across studies [6]. In one of these cases, immunohistological analysis of the arterial wall revealed an infiltration of CD3⁺, CD56⁺ T cells [6]. Although the exact mechanisms responsible for aneurysmal degeneration after Eluvia™ implantation are not known, as with coronary arteries, vascular inflammation might be associated with this syndrome.

Eluvia™ is coated with the primer polymer poly (n-butyl methacrylate) and an active layer composed of the matrix polymer poly (vinylidene fluoride-co-hexafluoropropylene). These coatings permit the elution of paclitaxel over approximately 12 months at a dose density of 0.167 µg paclitaxel per mm² stent surface area [4]. Farb et al. showed a dose-dependent increase in fibrin deposition and medial necrosis after deployment of paclitaxel-eluting stents in rabbit iliac arteries [12]. Another previous pathological report mentioned that the features of paclitaxel-eluting stent implantation included excessive para-strut fibrin deposition and incomplete stent apposition in patients with late stent thrombosis, suggesting that paclitaxel itself was responsible [13]. In fact, although Zilver PTX™ is a paclitaxel-coated stent without polymer, some clinical reports also recorded cases with PSS on angiography or extra stent lumen enlargement on serial optical coherence tomography after Zilver PTX™ implantation at later times [14, 15]. Therefore, it is possible that paclitaxel itself similarly induces vascular inflammation after Eluvia™ implantation and may contribute to aneurysmal degeneration. It has been reported that the polymer coatings could also cause increased vessel inflammation, which is sometimes severe, even leading to medial disruption and aneurysm [16-18]. Pathological studies regarding vascular responses to Zilver PTX™ versus Eluvia™ showed higher inflammatory reactions around struts in the latter 1-, 3-, 6- and 12-months after implantation, possibly caused by continuous exposure to paclitaxel, or the presence of the durable polymer coating [19]. Furthermore, 24-month results of the IMPERIAL randomized trial showed hypoechogenic halo suggestive of aneurysmal degeneration in 33.7% of patients after Eluvia™ implantation and 21.4% after Zilver PTX™ implantation, but this difference was not statistically significant [5]. The frequency of aneurysmal degeneration 24 months after Eluvia™ implantation increased compared to what was seen at 12 months [4, 5]. Thus, although there was no significant difference, the frequency of occurrence of aneurysmal degeneration tended to be greater for Eluvia™ than Zilver PTX™ [5]. Judging from these results, the durable polymer employed by Eluvia™ might be associated with more vessel inflammation, resulting in aneurysmal degeneration at later times. According to the manufacturers of the stent platforms, the constant outward self-expanding force is greater in Eluvia™ than Zilver PTX™, which itself might contribute to vessel inflammation,

Although data on the clinical parameters of patients with aneurysmal degeneration in PAD are scarce, a previous report on coronary artery disease showed that PSS found within 12 months after DES implantation was potentially associated with subsequent target lesion revascularization and very late

stent thrombosis [7]. Bisdas et al. reported that 5 of 62 patients treated by Eluvia™ implantation had aneurysmal degeneration and one of these presented with clinical worsening caused by the occlusion of the stent [6]. Given these data, long-term follow-up should be mandatory for patients receiving Eluvia™ implantation. Further investigation is warranted to evaluate the impact of aneurysmal degeneration after Eluvia™ implantation on clinical outcomes. Although dual antiplatelet therapy is recommended for at least 60 days after Eluvia™ implantation, its prolongation might be worth considering in patients with aneurysmal degeneration.

Conclusions

We report a case with exacerbated aneurysmal degeneration on serial angiography and intravascular ultrasound 50 months after Eluvia™ implantation for an SFA lesion. Long-term follow-up should be mandatory for patients receiving Eluvia™ implants.

Abbreviations

ABI: Ankle brachial index

DES: Drug-eluting stent

EVT: Endovascular therapy

IVUS: Intravascular ultrasound

PSS: Peri-stent contrast staining

SFA: Superficial femoral artery

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendment or comparable ethical standards. Patient's specific consent was obtained for this report, and consent by the Institutional Review Board was not required.

Consent for publication

Consent for publication was obtained from the patients for publication of this case report and any accompanying images.

Availability of data and materials

Not applicable.

Competing interests

O.I. has a remuneration from Medtronic Japan and Boston scientific Japan, and T.M. has a research grant from Abbott vascular Japan. T.T. have no disclosures to report.

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Authors' contributions

All authors have made substantial contributions to all of the following: 1) conception and design and interpretation of data, or both; 2) drafting of the manuscript or revising it critically for important intellectual content; and 3) final approval of the manuscript submitted.

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References

1. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I; ESC Scientific Document Group (2018) 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J* 39:763-816.
2. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME (2017) 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 69:1465-1508.
3. Conte MS, Pomposelli FB, Clair DG, Geraghty PJ, McKinsey JF, Mills JL, Moneta GL, Murad MH, Powell RJ, Reed AB, Schanzer A, Sidawy AN (2015) Society for Vascular Surgery. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: Management of asymptomatic disease and claudication. *J Vasc Surg* 61:2S-41S.

4. Gray WA, Keirse K, Soga Y, Benko A, Babaev A, Yokoi Y, Schroeder H, Prem JT, Holden A, Popma J, Jaff MR, Diaz-Cartelle J, Müller-Hülsbeck S (2018) IMPERIAL investigators. A polymer-coated, paclitaxel-eluting stent (Eluvia) versus a polymer-free, paclitaxel-coated stent (Zilver PTX) for endovascular femoropopliteal intervention (IMPERIAL): a randomised, non-inferiority trial. *Lancet* 392:1541-1551.
5. Müller-Hülsbeck S, Benko A, Soga Y, Fujihara M, Iida O, Babaev A, O'Connor D, Zeller T, Dulas DD, Diaz-Cartelle J, Gray WA (2021) Two Year Efficacy and Safety Results from the IMPERIAL Randomized Study of the Eluvia Polymer-Coated Drug-Eluting Stent and the Zilver PTX Polymer-free Drug-Coated Stent. *Cardiovasc Intervent Radiol* 44:368-375.
6. Bisdas T, Beropoulis E, Argyriou A, Torsello G, Stavroulakis K (2018) 1-Year All-Comers Analysis of the Eluvia Drug-Eluting Stent for Long Femoropopliteal Lesions After Suboptimal Angioplasty. *JACC Cardiovasc Interv* 11:957-966.
7. Imai M, Kadota K, Goto T, Fujii S, Yamamoto H, Fuku Y, Hosogi S, Hirono A, Tanaka H, Tada T, Morimoto T, Shiomi H, Kozuma K, Inoue K, Suzuki N, Kimura T, Mitsudo K (2011) Incidence, risk factors, and clinical sequelae of angiographic peri-stent contrast staining after sirolimus-eluting stent implantation. *Circulation* 123:2382-2391.
8. Tokuda T, Yamawaki M, Takahara M, Mori S, Makino K, Honda Y, Takafuji H, Takama T, Tsutsumi M, Sakamoto Y, Takimura H, Kobayashi N, Araki M, Hirano K, Ito Y (2016) Comparison of Long-Term Clinical Outcomes of Lesions Exhibiting Focal and Segmental Peri-Stent Contrast Staining. *J Am Heart Assoc.* 5(3):e002878. doi: 10.1161/JAHA.115.002878.
9. Virmani R, Liistro F, Stankovic G, Di Mario C, Montorfano M, Farb A, Kolodgie FD, Colombo A (2002) Mechanism of late in-stent restenosis after implantation of a paclitaxel derivate-eluting polymer stent system in humans. *Circulation* 106:2649-2651.
10. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, Mihalcsik L, Tsepili M, Valsecchi O, Kolodgie FD (2004) Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109:701-705.
11. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R (2006) Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol* 48:193-202.
12. Farb A, Heller PF, Shroff S, Cheng L, Kolodgie FD, Carter AJ, Scott DS, Froehlich J, Virmani R (2001) Pathological analysis of local delivery of paclitaxel via a polymer-coated stent. *Circulation* 104:473-479.
13. Nakazawa G, Finn AV, Vorpahl M, Ladich ER, Kolodgie FD, Virmani R (2011) Coronary responses and differential mechanisms of late stent thrombosis attributed to first-generation sirolimus- and paclitaxel-eluting stents. *J Am Coll Cardiol* 57:390-398.
14. Ikeoka K, Okayama K, Watanabe T, Nanto S, Sakata Y, Hoshida S (2018) Refractory Vascular Wall Healing after Paclitaxel-Coated Nitinol Stent Implantation in the Femoropopliteal Artery: A High-Resolution Angioscopic Assessment. *Ann Vasc Dis* 11:373-376.

15. Tomoi Y, Kuramitsu S, Soga Y, Aihara H, Ando K, Nobuyoshi M (2015) Vascular response after Zilver PTX stent implantation for superficial femoral artery lesions: serial optical coherence tomography findings at 6 and 12 months. *J Endovasc Ther* 22:41-47.
16. van der Giessen WJ, Lincoff AM, Schwartz RS, van Beusekom HM, Serruys PW, Holmes DR Jr, Ellis SG, Topol EJ (1996) Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 94:1690-1697.
17. Byrne RA, Joner M, Kastrati A (2009) Polymer coatings and delayed arterial healing following drug-eluting stent implantation. *Minerva Cardioangiol* 57:567-584.
18. John MC, Wessely R, Kastrati A, Schömig A, Joner M, Uchihashi M, Crimins J, Lajoie S, Kolodgie FD, Gold HK, Virmani R, Finn AV (2008) Differential healing responses in polymer- and nonpolymer-based sirolimus-eluting stents. *JACC Cardiovasc Interv* 1:535-544.
19. Sakamoto A, Torii S, Jinnouchi H, Fuller D, Cornelissen A, Sato Y, Kuntz S, Mori M, Kawakami R, Kawai K, Fernandez R, Paek KH, Gadhok N, Guo L, Kolodgie FD, Young B, Ragheb A, Virmani R, Finn AV (2021) Vascular Response of a Polymer-free, Paclitaxel-coated Stent (Zilver PTX) Versus a Polymer-coated, Paclitaxel-eluting Stent (Eluvia) in Healthy Swine Femoropopliteal Arteries. *J Vasc Interv Radiol*. doi: 10.1016/j.jvir.2021.02.014.

Figures

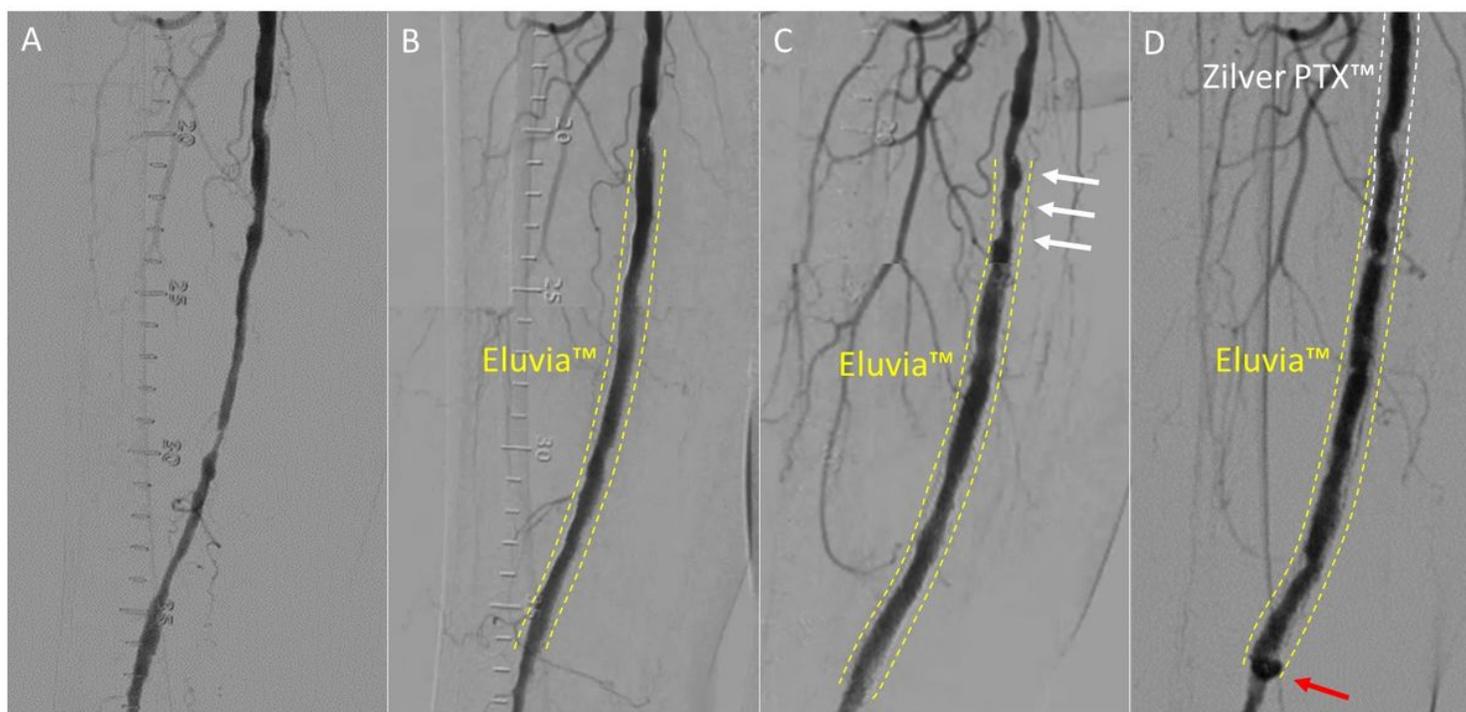


Figure 1

Angiographs A: Initial angiography Initial angiography revealing a severe stenosis from the middle-to-distal part of the right superficial femoral artery. B: Angiography immediately after Eluvia™ implantation

Angiography showing optimal expansion after Eluvia™ implantation. C: Angiography 25 months after Eluvia™ implantation. Angiography revealing proximal stent edge restenosis at the Eluvia™ implantation site (white arrows). D: Angiography 50 months after Eluvia™ implantation. Angiography documenting peri-stent contrast staining at the distal part of the Eluvia™ implantation site (red arrow).

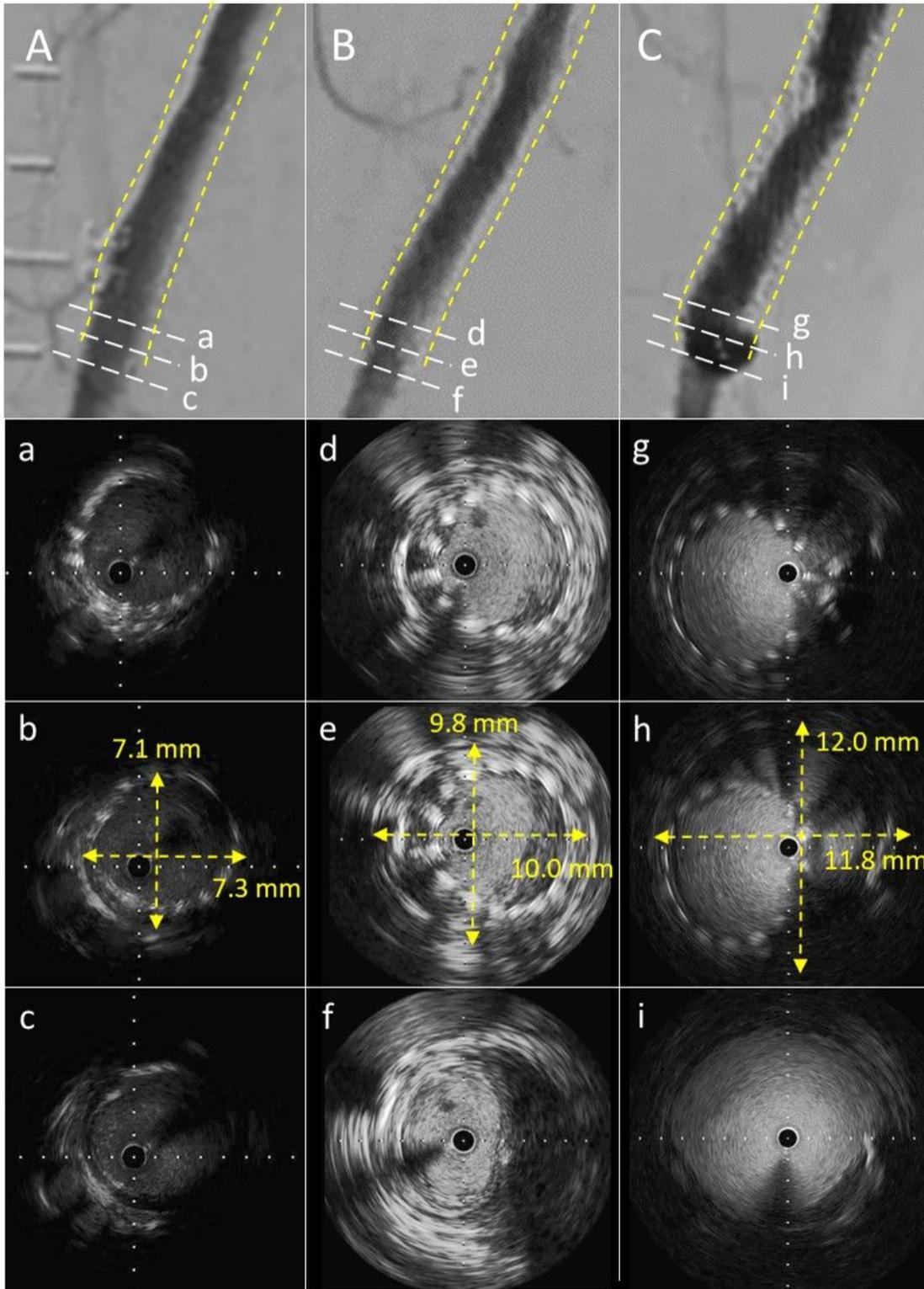


Figure 2

Angiographs and intravascular ultrasound (IVUS) immediately, 25 months, and 50 months after Eluvia™ implantation. A: Angiography immediately after Eluvia™ implantation Angiography showing optimal expansion. B: Angiography 25 months after Eluvia™ implantation Angiography showing no significant stenosis or peri-stent contrast staining in the distal part of the right superficial femoral artery. C: Angiography 50 months after Eluvia™ implantation Angiography demonstrating peri-stent contrast staining in the distal part of the Eluvia™ implantation site. a-c: Images of IVUS immediately after Eluvia™ implantation. IVUS demonstrating optimal expansion of Eluvia™ (a-c). Mean vessel diameter was 7.2 mm at the distal edge of the Eluvia™ implantation site (b). d-f: Images of IVUS 25 months after Eluvia™ implantation. IVUS revealing vessel enlargement with a mean vessel diameter of 9.9 mm at the distal edge of the Eluvia™ implantation site (d-f). g-i: Images of IVUS 50 months after Eluvia™ implantation. IVUS showing further enlargement of the mean vessel diameter to 11.9 mm at the distal edge of the Eluvia™ stent (g-i). Enlargement of the lumen and stent malapposition (g and h).