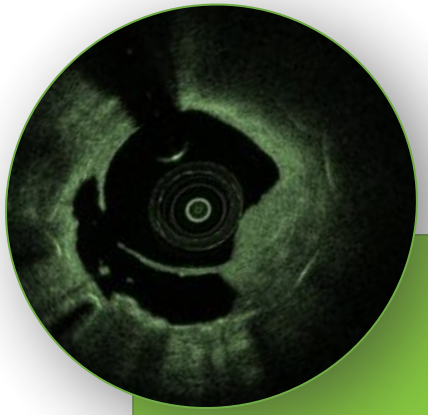
APPAC
6/7/8 Juin 2018
Palais des Congrès de Biarritz

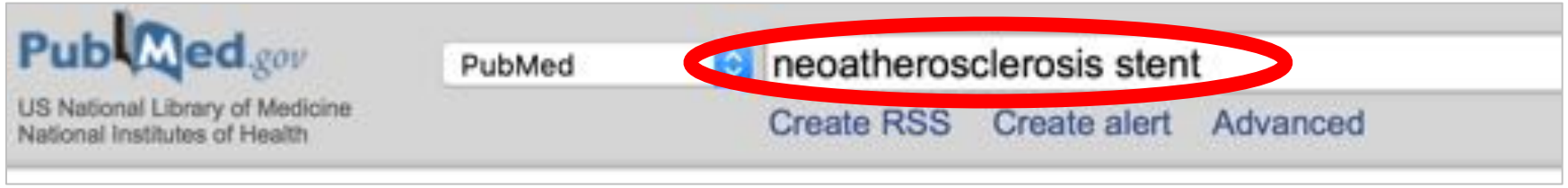


Néoathérosclérose ou Athérosclérose Intrastent

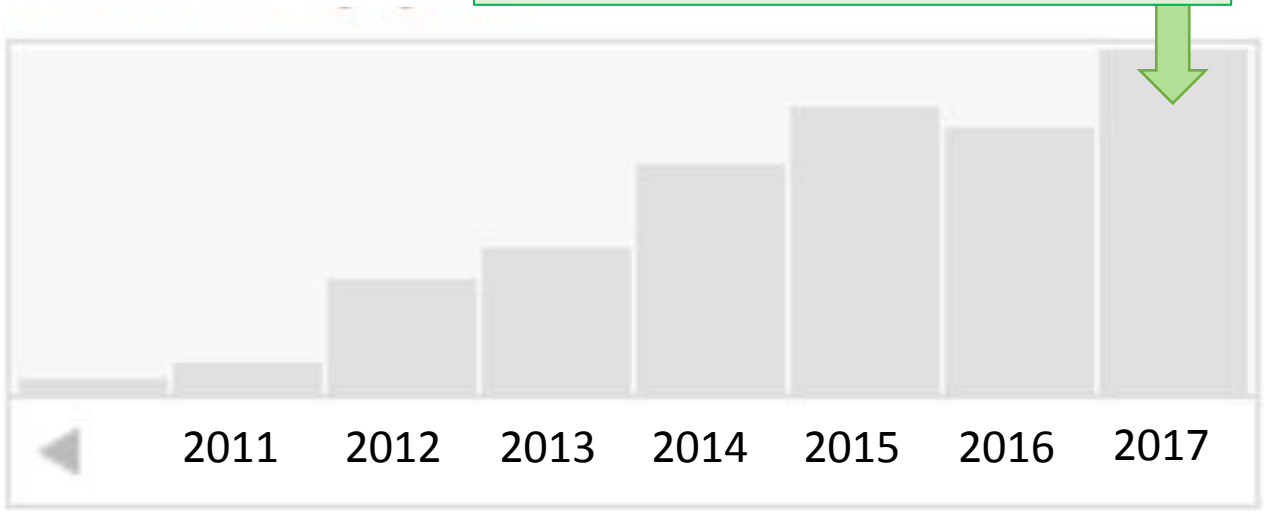
Pascal MOTREFF

Conflits d'intérêts : consulting Abbott, Terumo

Néoathérosclérose



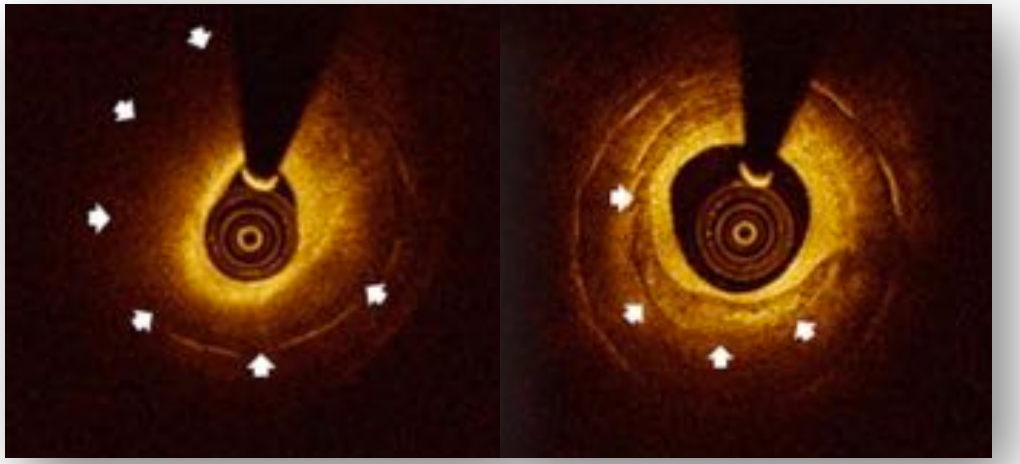
50 publications en 2017



- **Physiopathologie**
- **Facteurs de risque**
- **Diagnostic**
- **Impact clinique**
- **Gestion**

Néoathérosclérose

Définition

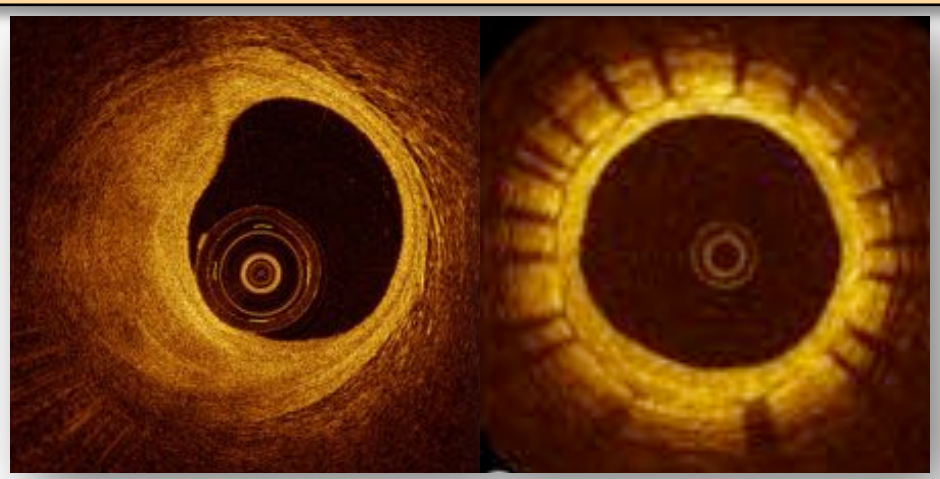


Athérosclérose intrastent

accumulation de macrophages riches en lipide au niveau de la néointima
formation d'un core nécrotique +/- calcifications intrastent

≠ Athérosclérose de novo

≠ Hyperplasie néointimale

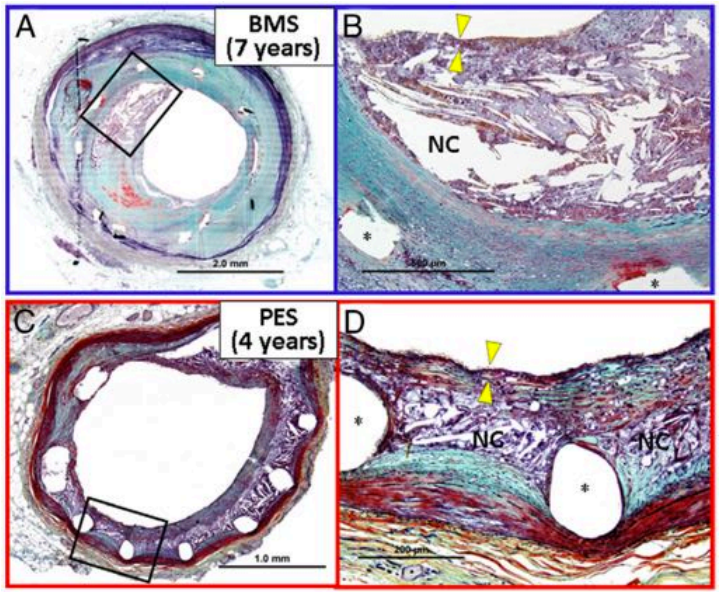


Lee SY, Circ Interv 2015

Néoathérosclérose

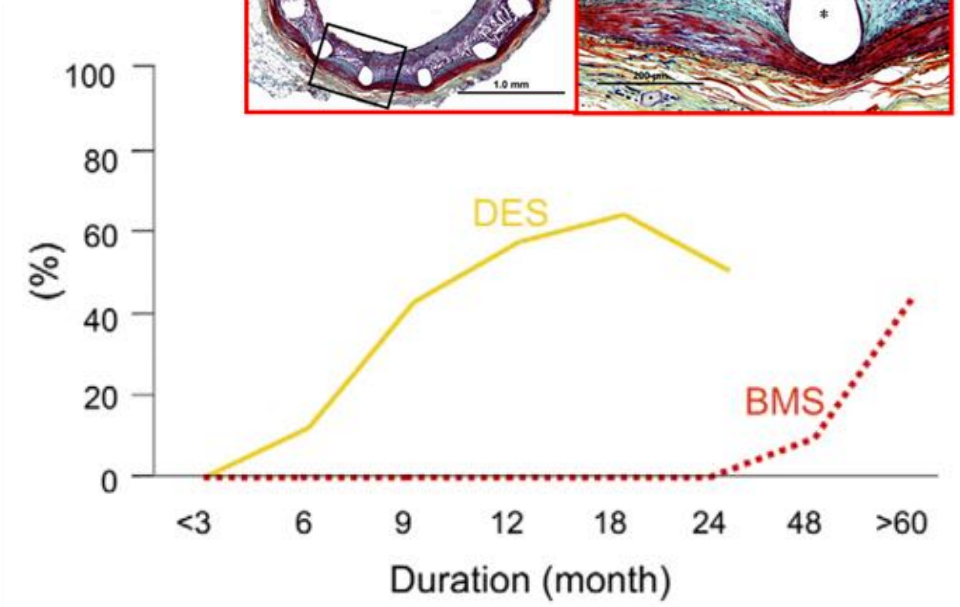
In-Stent Neoatherosclerosis

A Final Common Pathway of Late Stent Failure



-Responsable **<u>complications tardives</u>** +++ (>1 an)
-Plus fréquente avec DES
-Plus précoce avec DES

-Mécanismes mal connus
-Plus fréquente en proximal qu'en distal
-Apport de l'imagerie endocoronaire



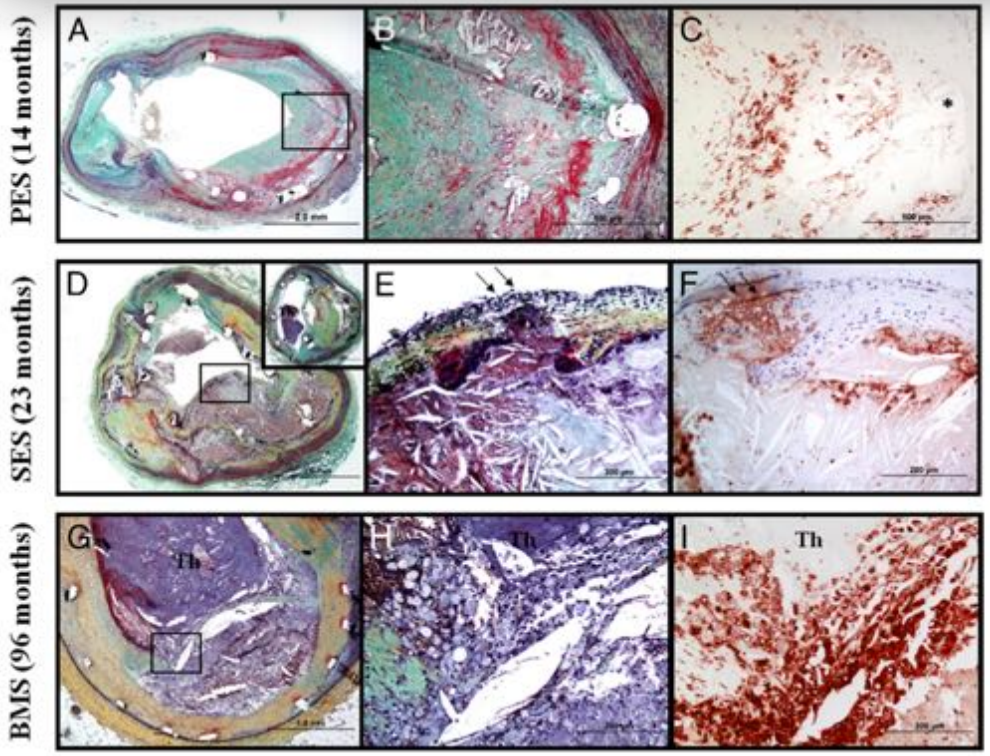
Park SJ, J Am Coll Cardiol 2012

Yahagi K, Nat. Rev. Cardiol. 2015

Néoathérosclérose

The Pathology of Neoatherosclerosis in Human Coronary Implants

Bare-Metal and Drug-Eluting Stents

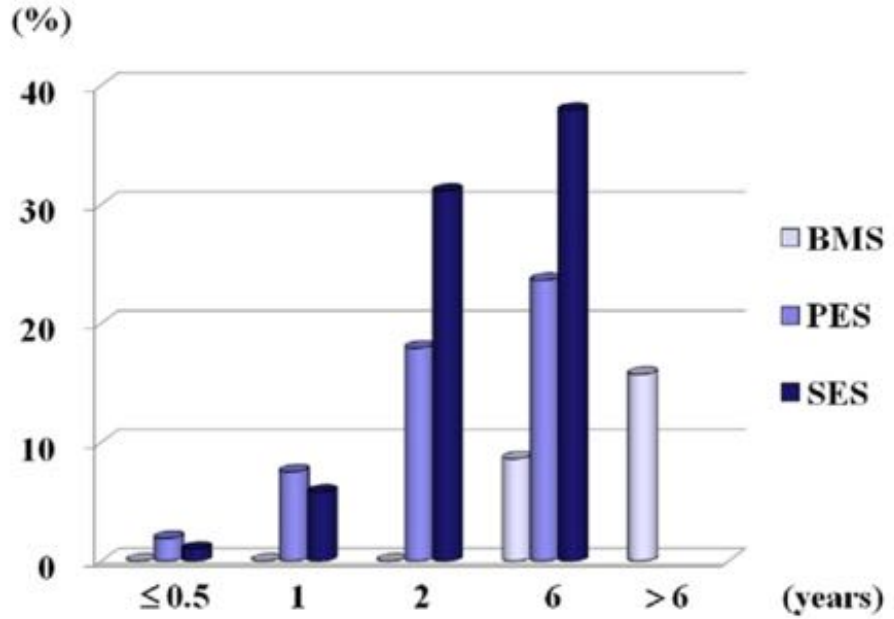


<u>299 autopsies</u> (406 stents)

Néoathérosclérose : **31% DES vs 16% BMS**

Age du stent en cas de néoathérosclérose

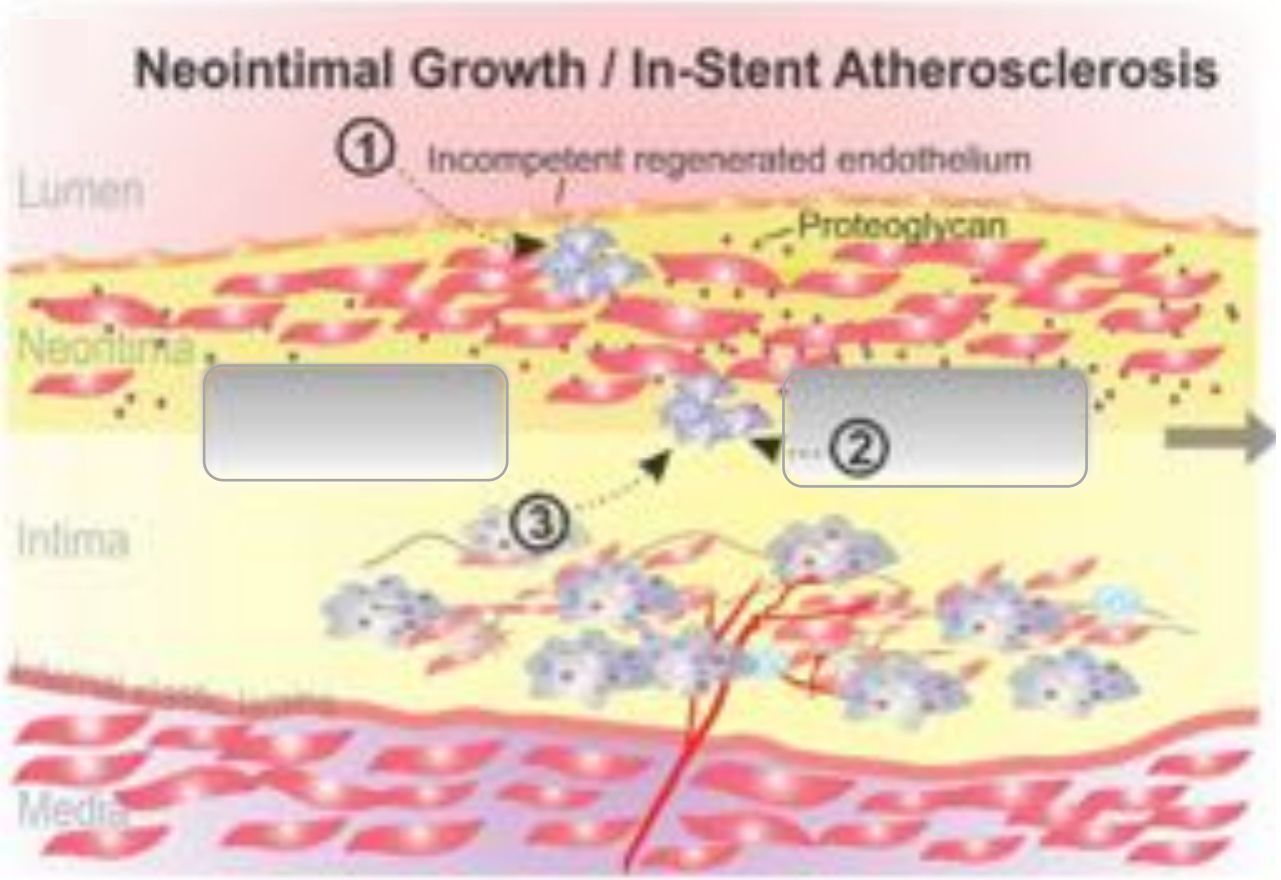
420j pour DES, **2160j** pour BMS



Nakazawa G, J Am Coll Cardiol 2011

Néoathérosclérose

Physiopathologie



Potential Mechanisms of In-Stent Atherosclerosis

① Absent or dysfunctional endothelium due to endothelial denudation poststenting, eluted drug-induced inhibition of reendothelialization, and disturbed flow-induced upregulation of proinflammatory genes might favor a greater lipid diffusion and inflammatory cell migration into (neo)intima in a similar, but potentially accelerated manner as the one depicted in panel A promoting neoatherosclerosis development

② Chronic foreign body inflammatory reaction to metal/polymer of stent struts with subsequent neovascularization and macrophage recruitment might enhance neoatherosclerosis development

③ The underlying native atherosclerotic plaque might contribute to in-stent atherosclerotic lesion either directly via expansion through stent struts or indirectly via release of growth factors and chemoattractants

Andreou I, Circulation 2016

Néoathérosclérose

TYPE DE STENT	BMS	DES 1ère G	DES 2ème G	BRS
Struts	**Epaisses**	**Epaisses**	Fines	**Epaisses**
Drogue	0	Dérivés Rapamycine / Paclitaxel	Dérivés Rapamycine	0 / Dérivés Rapamycine
Polymère	0	Durable	Durable / Biodégradable	0 / Biodégradable
Inflammation	Faible	Forte	Modérée	Modérée
Début de la Néoathérosclérose	Après 4 ans	SES : 70j PES : 120j	CoCr EES : 270j	?

Data modified from Inoue *et al*[33], Nakazawa *et al*[39], Otsuka *et al*[65]. DES: Drug-eluting stent; BRS: Bio-resorbable scaffold; SES: Sirolimus-eluting stent; PES: Paclitaxel-eluting stent.

Komiyama H, World J Cardiol. 2015

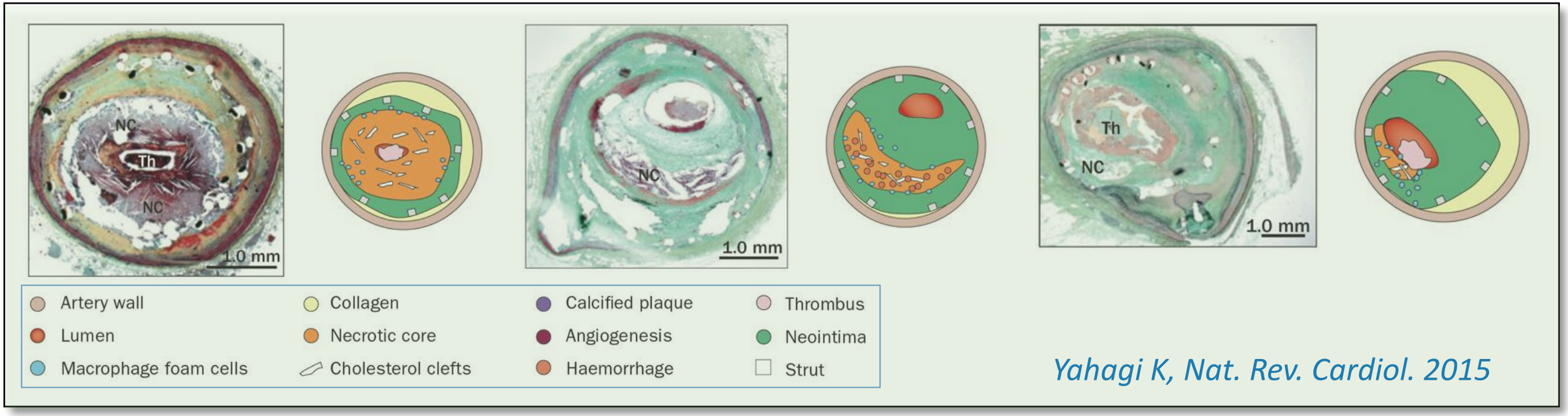
Néoathérosclérose

Physiopathologie

-Proche de l'athérosclérose accélérée des ponts saphènes

-Mécanismes de déstabilisation idem athérosclérose natif

- *Rupture de TCFA*
- *Hémorragie intraplaque (fragilité des vasa vasorum en péristrut)*



Yahagi K, Nat. Rev. Cardiol. 2015

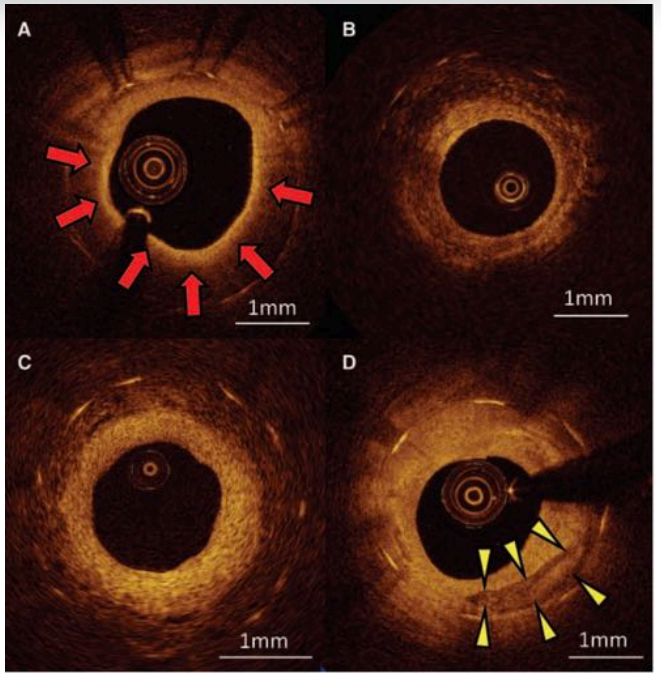
Néoathérosclérose

Facteurs de Risque

	Final Multivariate Model (n=179)		
	Adjusted Odds Ratio	95% CI	P
Stent age >48 mo	10.45	3.71–29.41	<0.001
DES			
SES	3.86	1.44–10.38	0.007
PES	24.17	6.02–97.02	<0.001
ZES	7.18	1.51–34.21	0.013
EES	6.46	1.65–25.34	0.007
BMS	1.00	…	…
Age>65 y	1.84	0.85–3.97	0.121
Hypertension	1.87	0.77–4.52	0.166
Hyperlipidemia	1.01	0.39–2.61	0.982
Diabetes mellitus	1.12	0.53–2.43	0.765
Smoking	7.03	2.46–20.04	<0.001
LDL-C>100 mg/dL			
TG>150 mg/dL			
CKD	3.69	1.10–12.35	0.035
Statin use	0.46	0.14–1.55	0.213
ACE-I/ARB use	0.39	0.17–0.91	0.028

Predictors for Neoatherosclerosis
A Retrospective Observational Study From the Optical Coherence Tomography Registry

- **Ancienneté du stent**
- **DES surtout 1ère génération**
- **Tabac**
- **Insuffisance rénale**
- **Protection : IEC/ARA II**



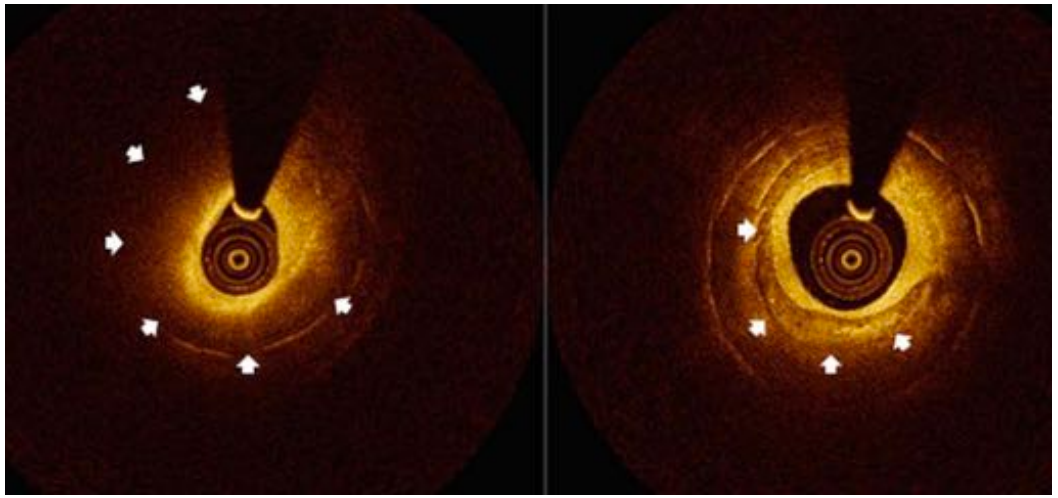
Yanetsu T, Circ Cardiovasc Imaging 2013

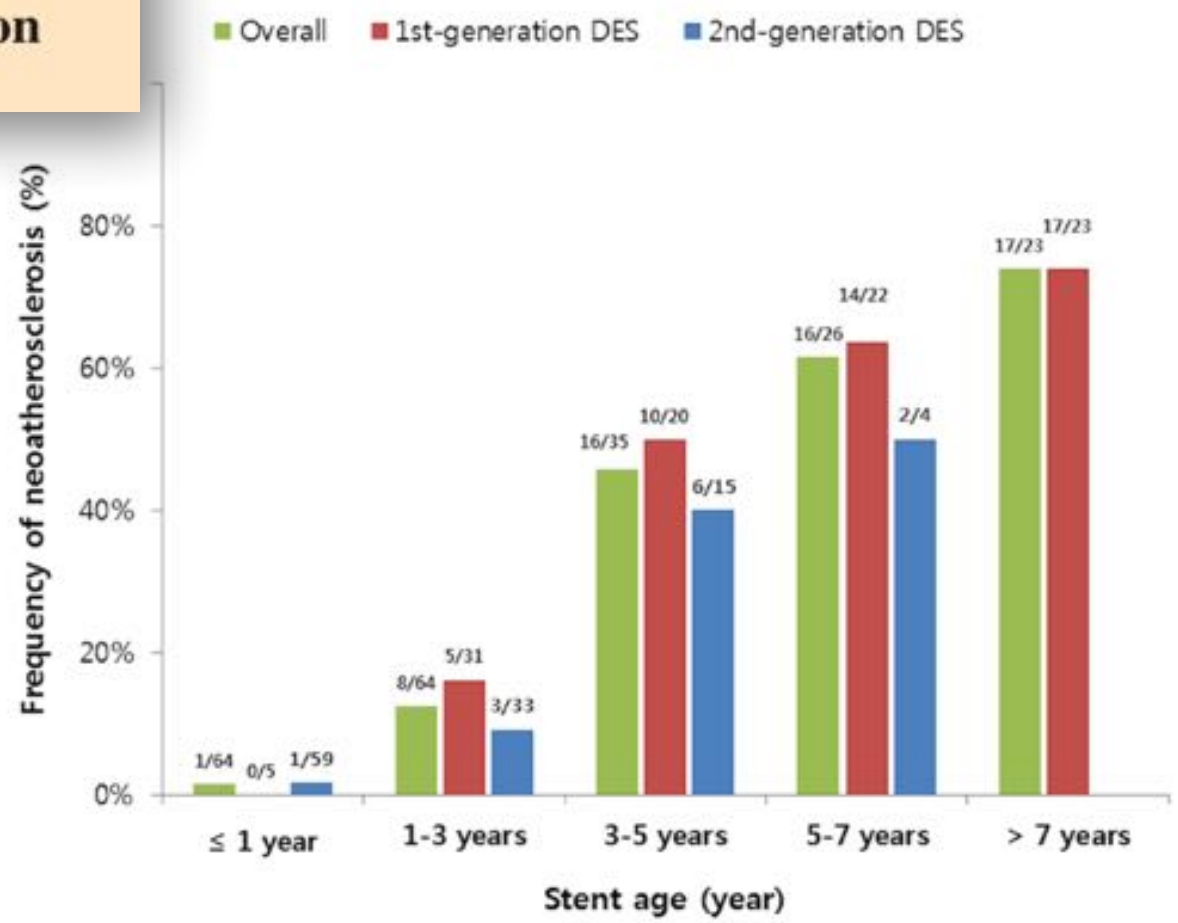
Néoathérosclérose

Facteurs de Risque

Optical Coherence Tomographic Observation of In-Stent Neoatherosclerosis in Lesions With More Than 50% Neointimal Area Stenosis After Second-Generation Drug-Eluting Stent Implantation

- The second-generation DES is not more protective against neoatherosclerosis compared with the first-generation DES.





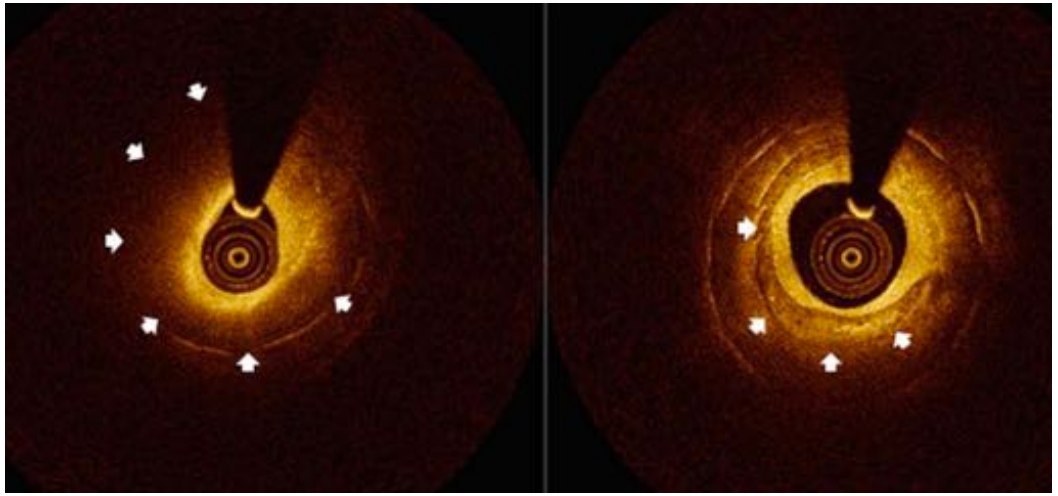
Lee SL, Circ Cardiovasc Interv 2015

Néoathérosclérose

Facteurs de Risque

Optical Coherence Tomographic Observation of In-Stent Neoatherosclerosis in Lesions With More Than 50% Neointimal Area Stenosis After Second-Generation Drug-Eluting Stent Implantation

- The second-generation DES is not more protective against neoatherosclerosis compared with the first-generation DES.
- More than 70 mg/dL of low-density cholesterol at follow-up was an independent predictor for neoatherosclerosis.



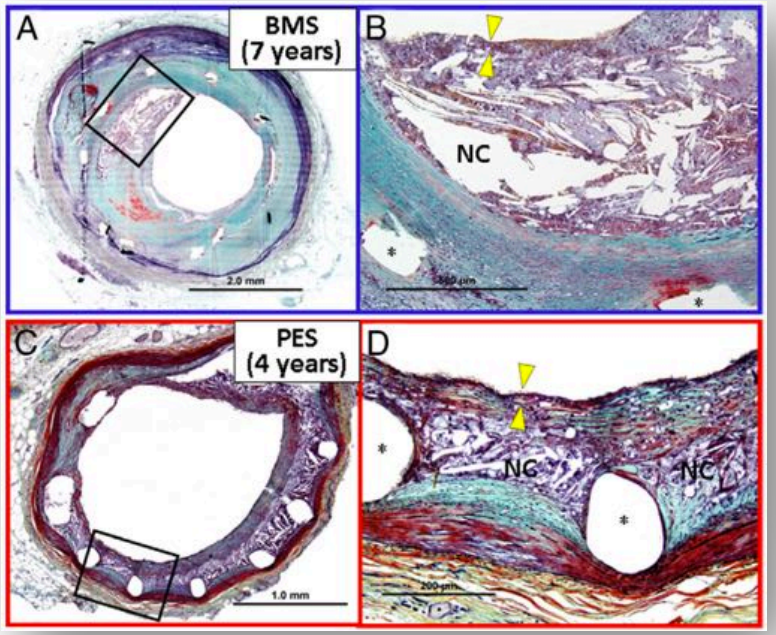
	Multivariable Analysis		
	Odds Ratio	95% CI	*P* Value
Baseline characteristics			
Age, y	1.017	0.969–1.067	0.50
Male	1.077	0.393–2.947	0.89
Hypertension	1.088	0.446–2.658	0.85
Diabetes mellitus	1.004	0.426–2.365	0.99
Chronic kidney disease	4.113	1.086–15.575	0.037
Usage of second-generation DES	0.538	0.196–1.481	0.23
Follow-up characteristics			
LDL cholesterol >70 mg/dL	2.532	1.054–6.084	0.038
Medication at follow-up			
ACE inhibitor or ARB	1.581	0.635–3.937	0.33
Statin	0.502	0.141–1.784	0.29
Stent age, y	1.710	1.403–2.084	<0.001

Lee SL, Circ Cardiovasc Interv 2015

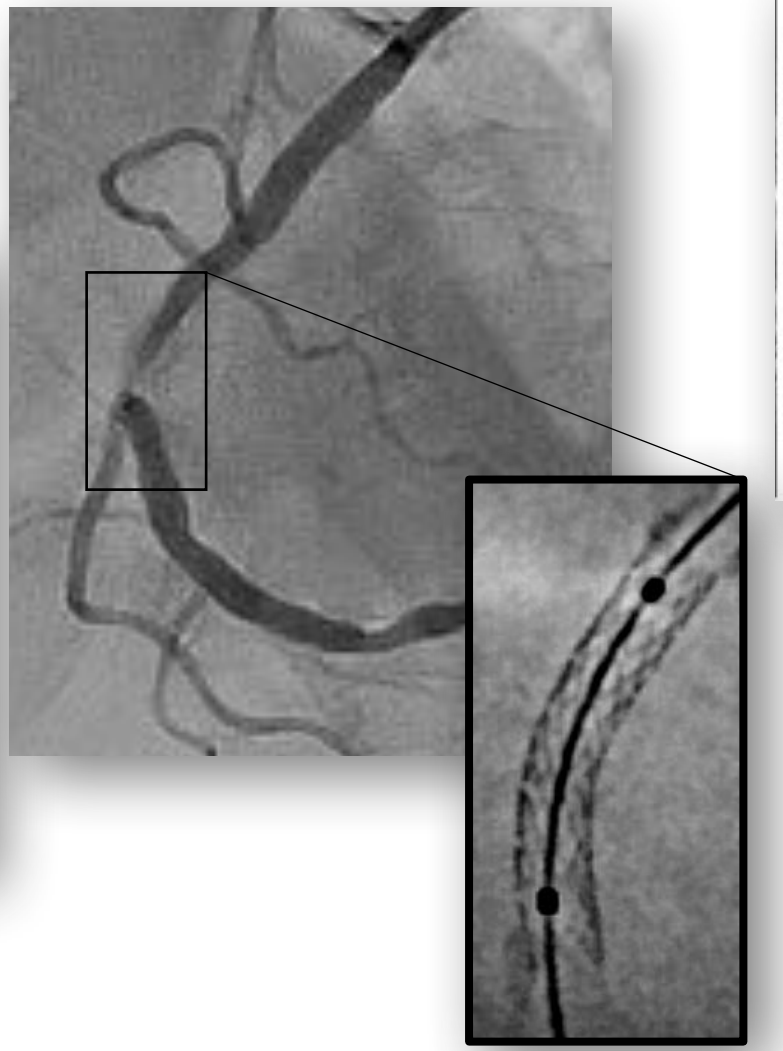
Néoathérosclérose

Diagnostic

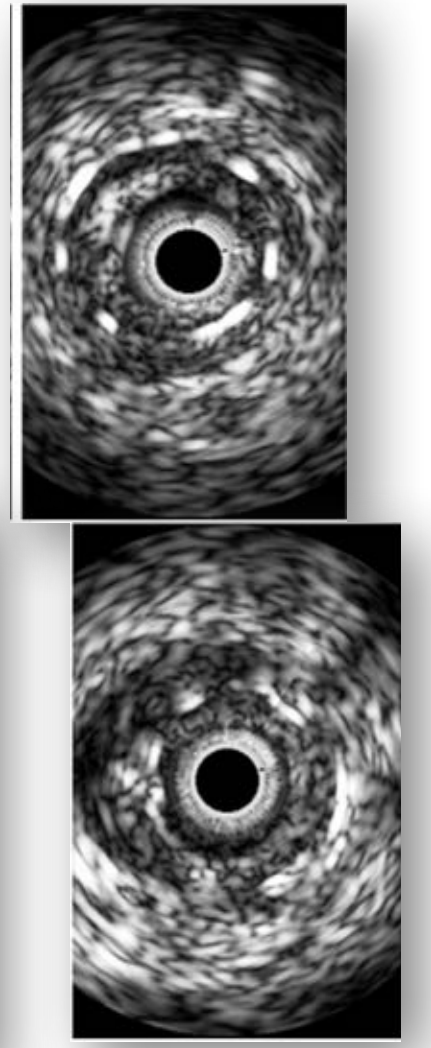
Anatomopathologie



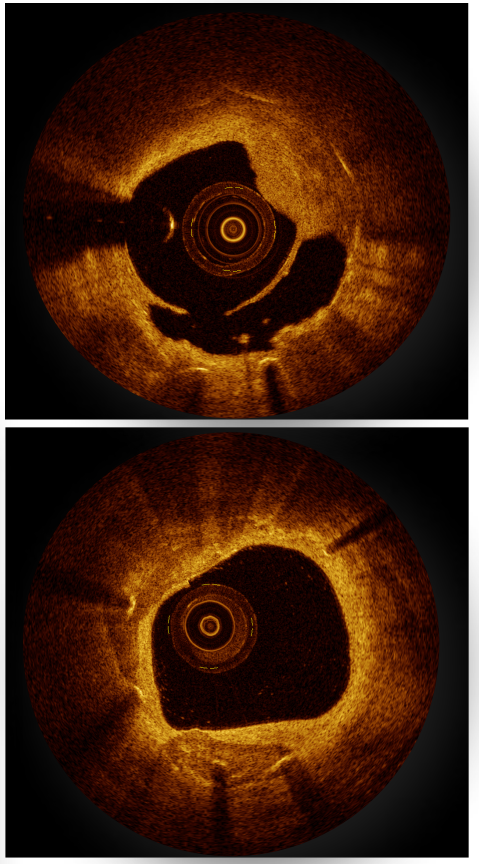
Coronarographie



IVUS

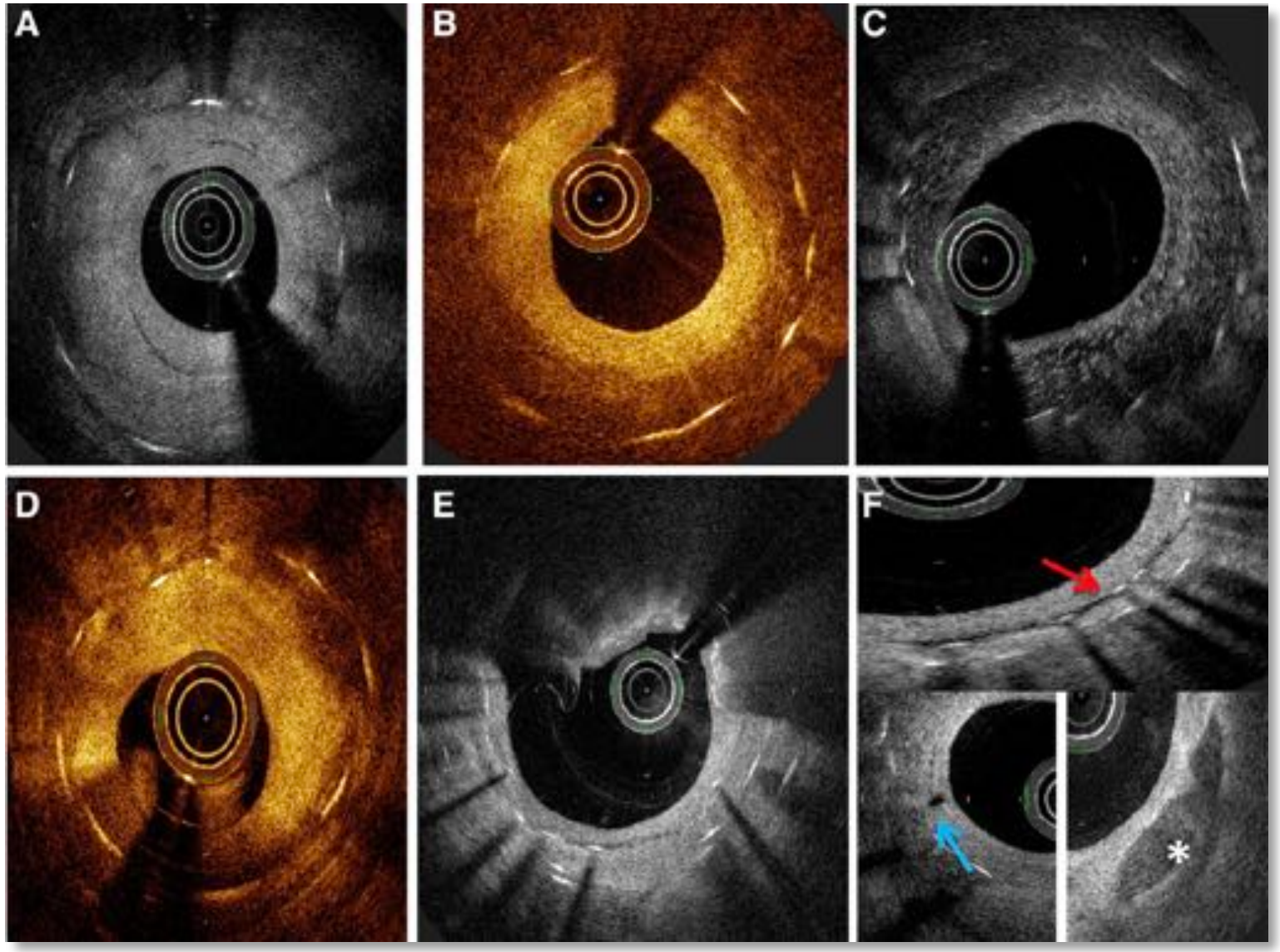


OCT



Néoathérosclérose

Diagnostic



Néoathérosclérose
Microvaisseaux
Calcification
PLIA

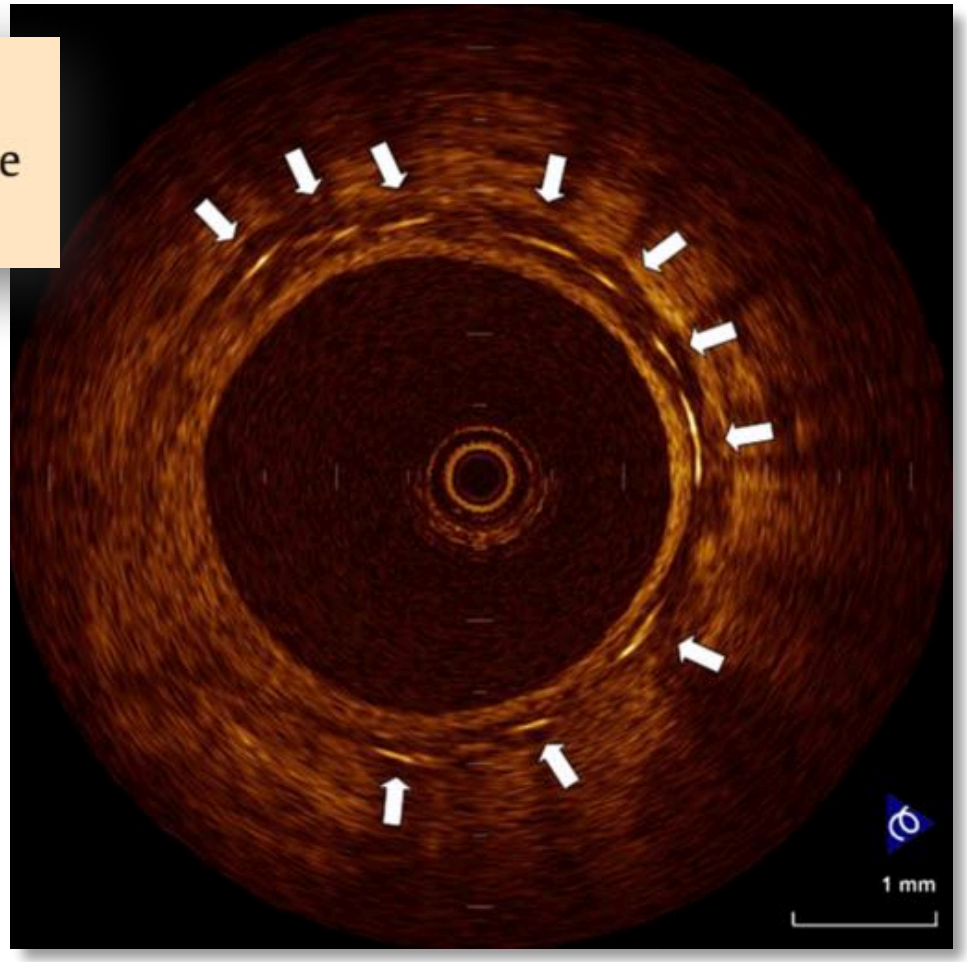
- Complications
  (rupture, thrombus)
- Diagnostics différentiels…

Sabbah M, Int J Cardiovasc Imaging 2017

Néoathérosclérose

Diagnostic

Evaluation of the peri-strut low intensity area following sirolimus- and paclitaxel-eluting stents implantation: Insights from an optical coherence tomography study in humans☆



PLIA = Peristrut Low Intensity Area

Accumulation fibrinogène
Matrice extracellulaire riche en protéoglycanes
Lien avec inflammation
Prédictif d'une néoathérosclérose
Plus fréquemment observé PES > SES >>> BMS

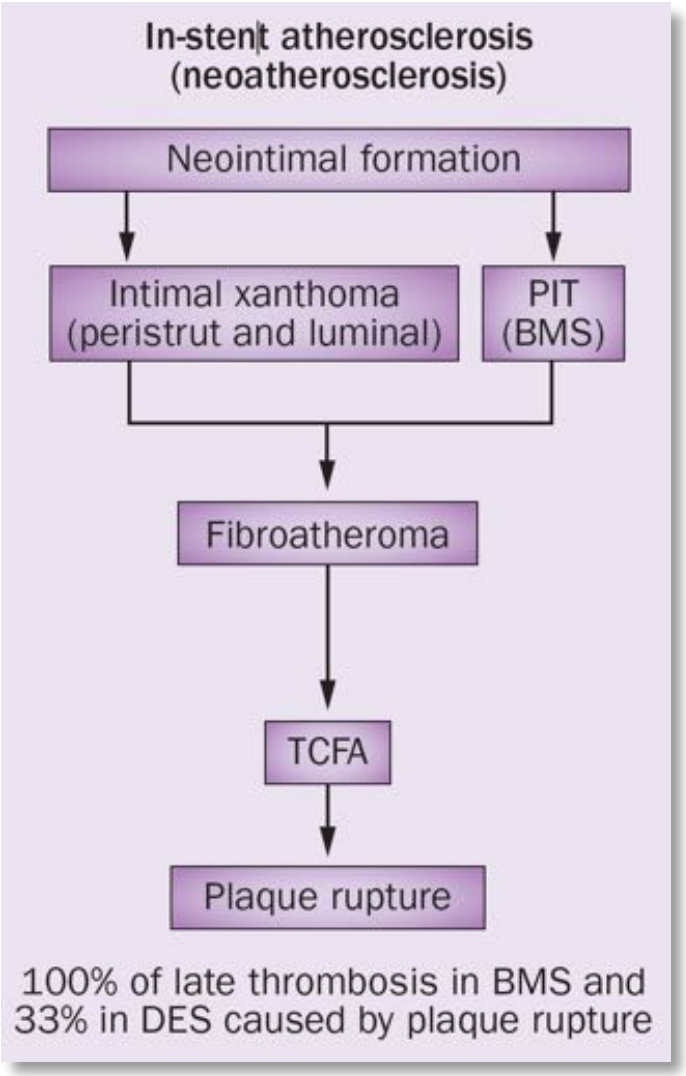
Otake H, Int J Cardiol 2010

Néoathérosclérose

Impact Clinique

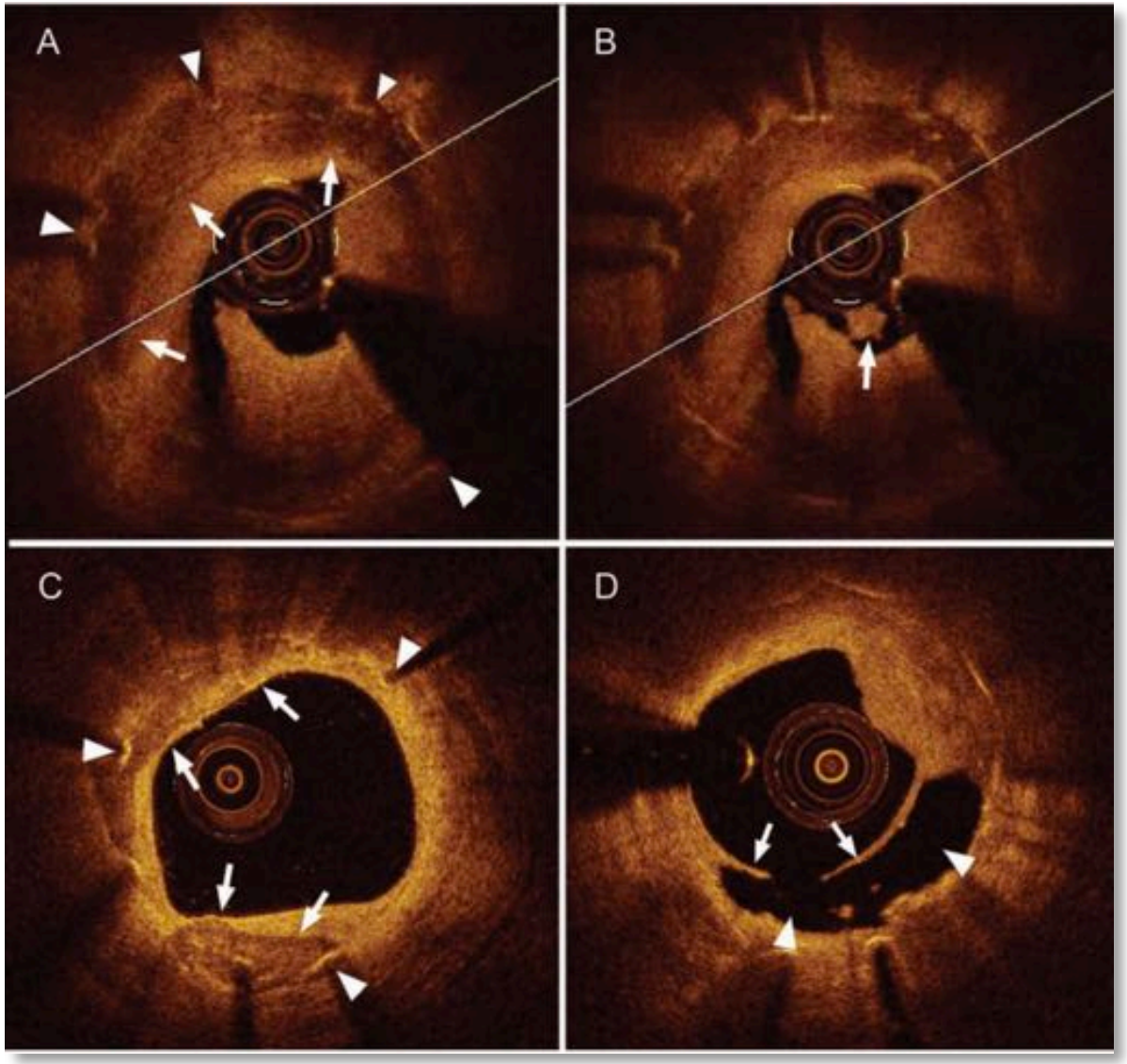
- **Resténose intrastent :**
  - 0-6 mois ≃ 0
  - 6-12 mois : Hyperplasie néointimale (BMS)
  - **>1 an : Néoathérosclérose +++ (BMS-DES)**

- **Thrombose intrastent :**
  - Aiguë (<24h)
  - Subaiguë (<1 mois)
  - **Tardive (<1 an)**
  - **Très tardive (> 1an)**



Yahagi K, Nat Rev Cardiol 2015

Néoathérosclérose



Thrombose intrastent

Very late stent thrombosis related to incomplete neointimal coverage or neoatherosclerotic plaque rupture identified by optical coherence tomography imaging

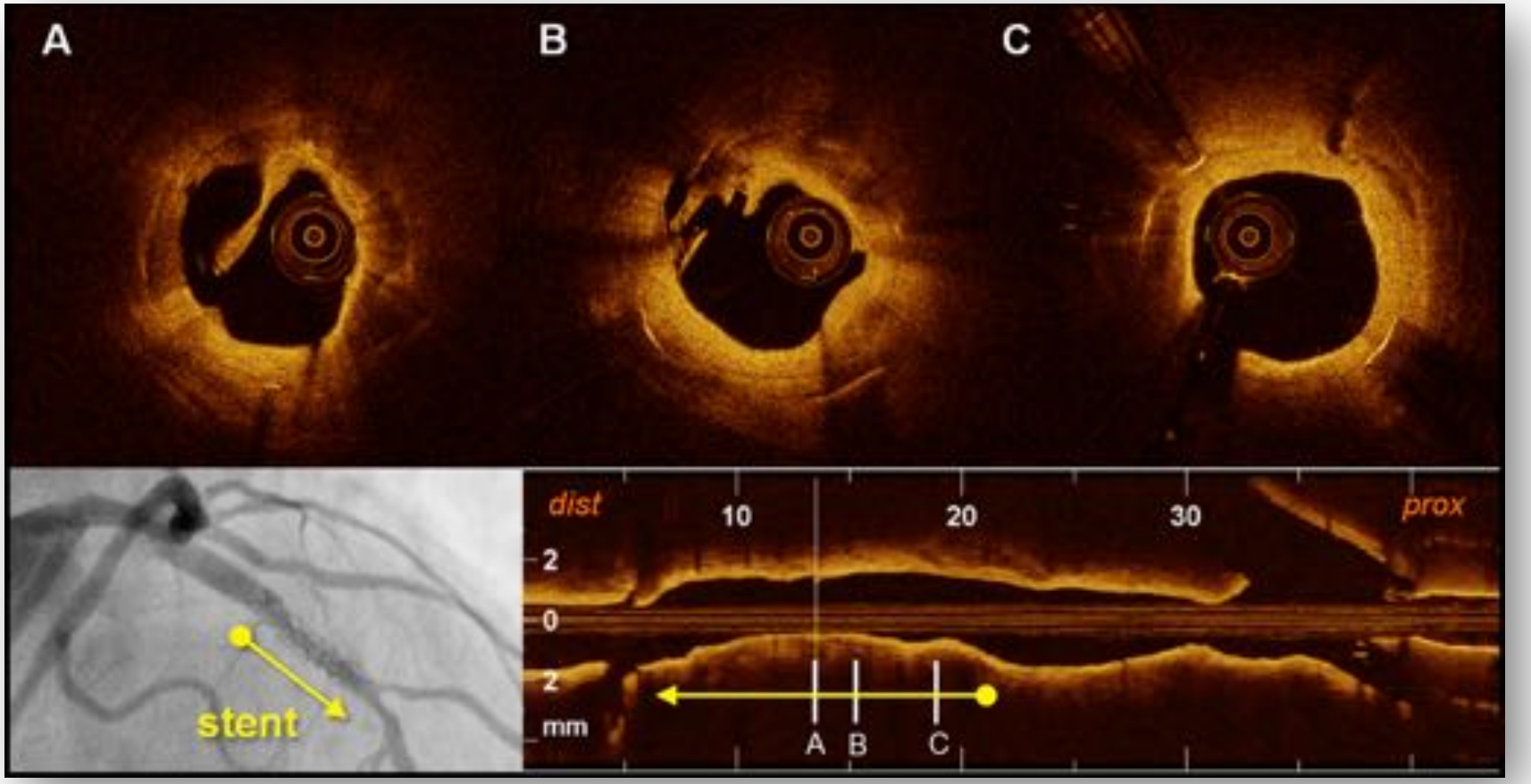
Nicolas Amabile[1*], Géraud Souteyrand[2,3], Said Ghostine[1], Nicolas Combaret[2,3], Michel S. Slama[4], Nicolas Barber-Chamoux[2,3], Pascal Motreff[2,3], and Christophe Caussin[1]

Amabile N, EHJ Cardiovasc Imaging 2013

Néoathérosclérose

Thrombose intrastent

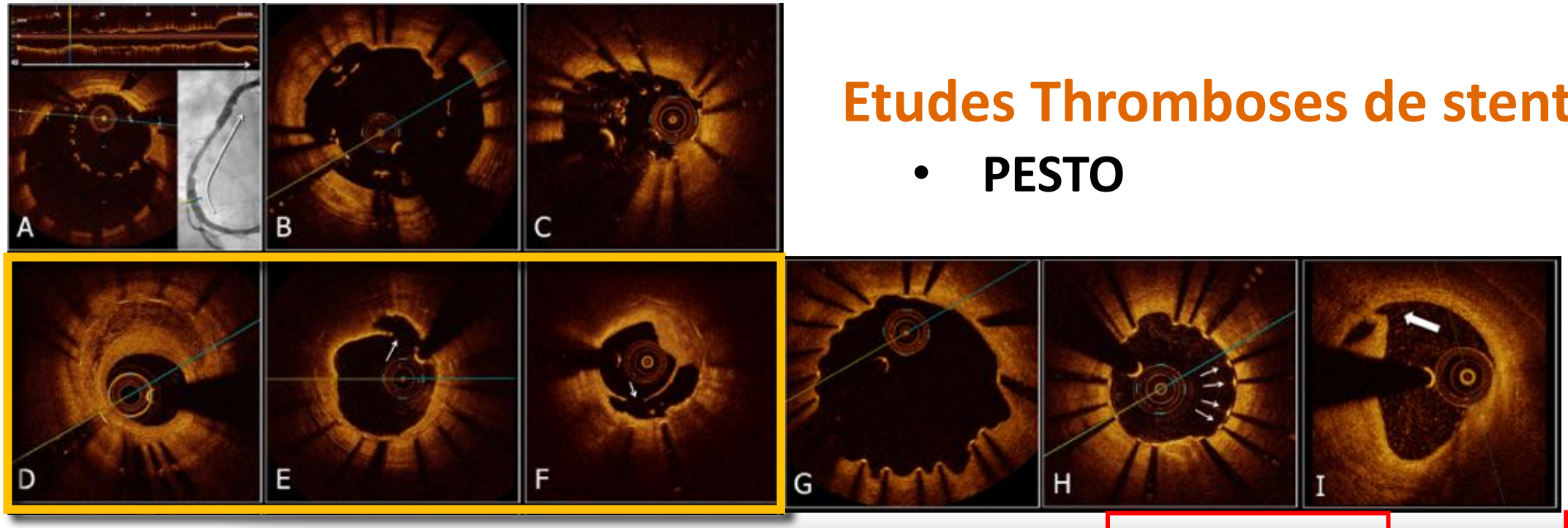
Rupture de néoathérosclérose intrastent



OCT F-U @ D3 after thrombus aspiration VLST

Motreff P, Souteyrand G

Néoathérosclérose



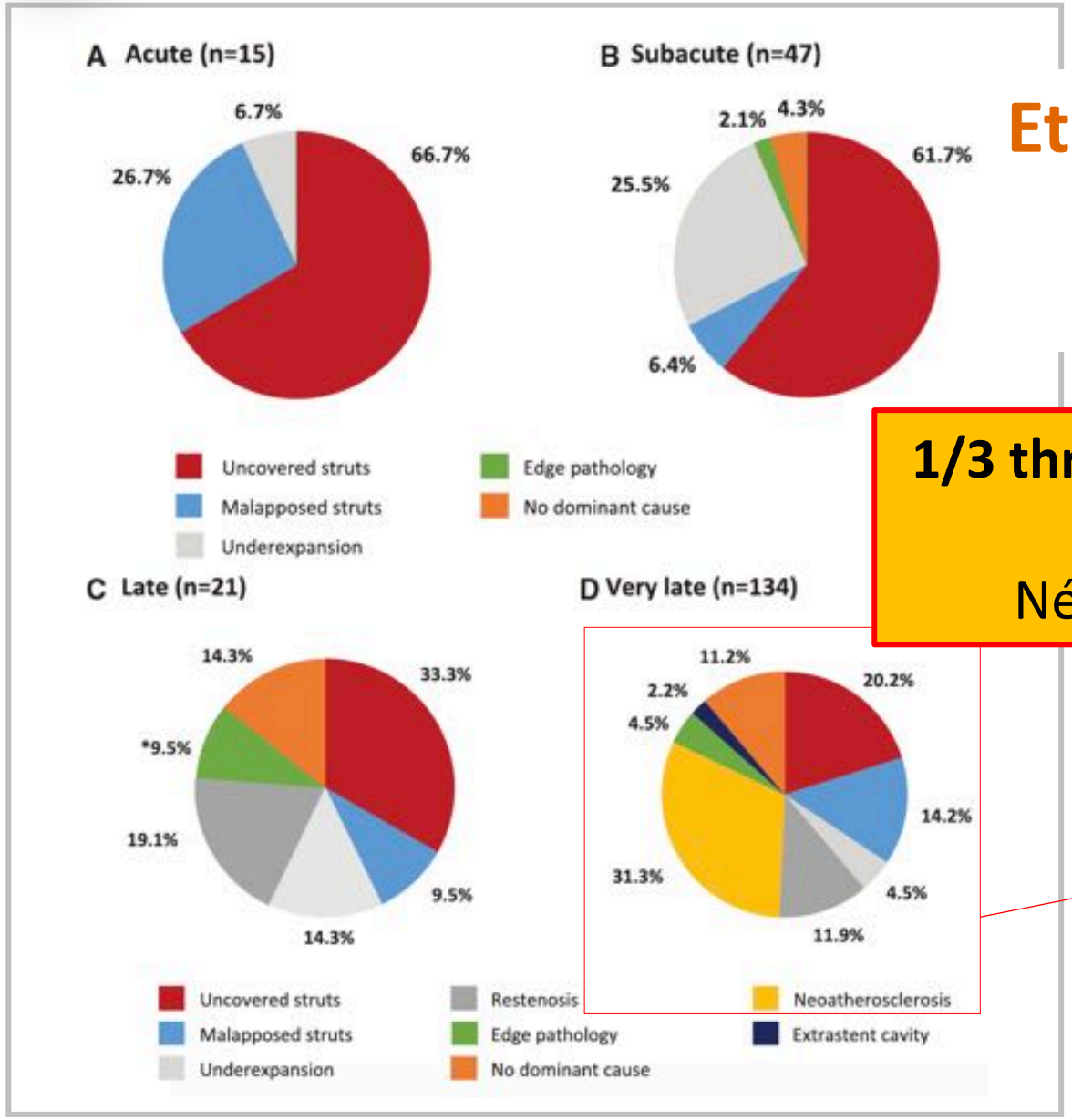
Etudes Thromboses de stents et OCT

- **PESTO**

	All patients (*n* = 120)	AST (*n* = 5)	SAST (*n* = 18)	LST (*n* = 7)	VLST (*n* = 90)	A + SAST (*n* = 23)	L + VLST (*n* = 97)
Malapposition (%)	34	60	44	44	30	48	32
Ruptured NA (%)	23	0	0	14	29	0	28
Severe underexpansion (%)	11	20	28	14	7	26	7

Souteyrand G, Eur Heart J 2016

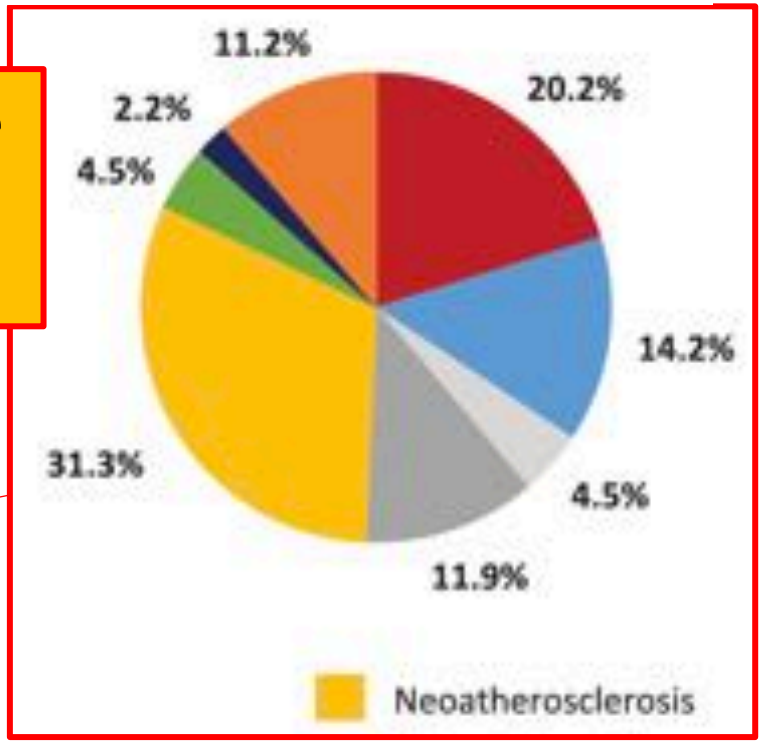
Néoathérosclérose



Etudes Thromboses de stents et OCT

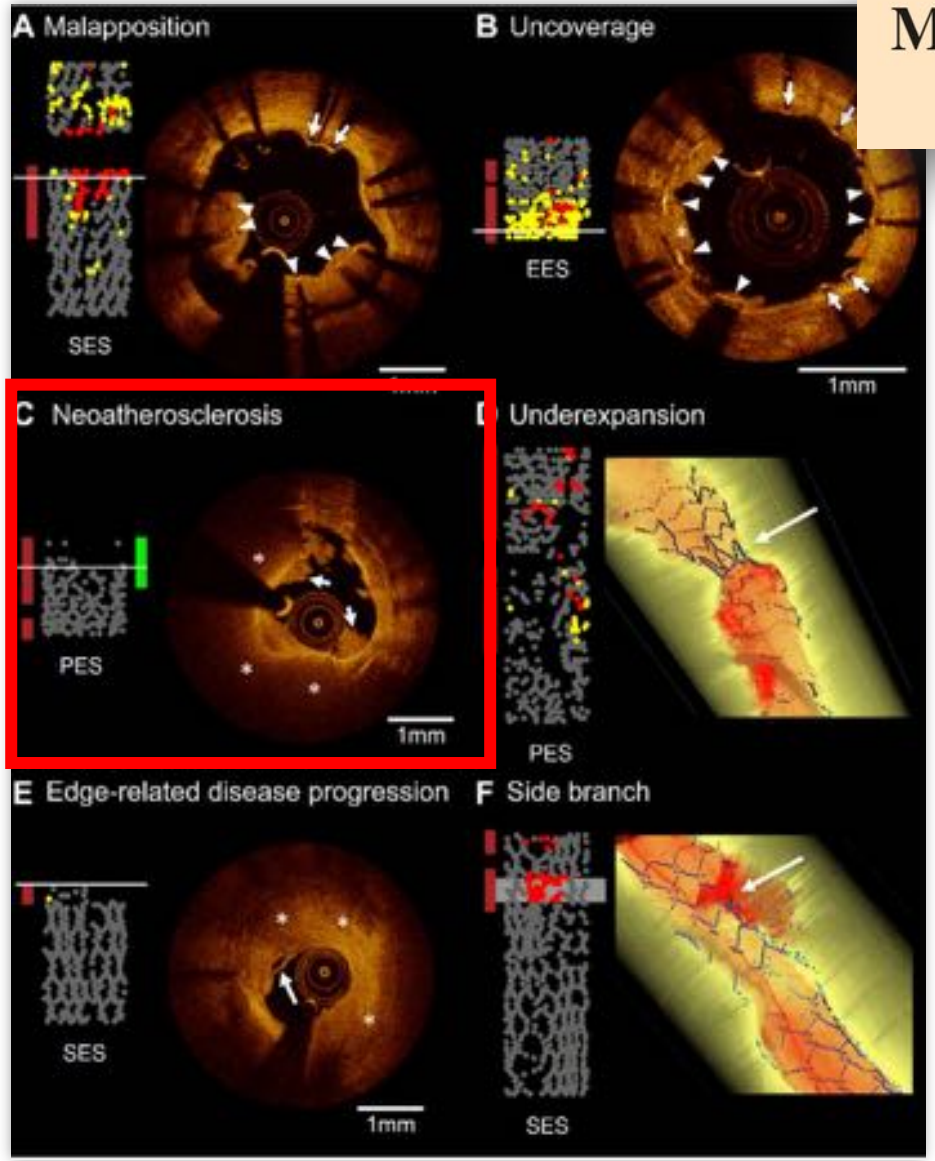
- PESTO
- **PRESTIGE**

1/3 thrombose très tardive est due à la Néoathérosclérose



Adriaenssens T, Circulation 2017

Néoathérosclérose



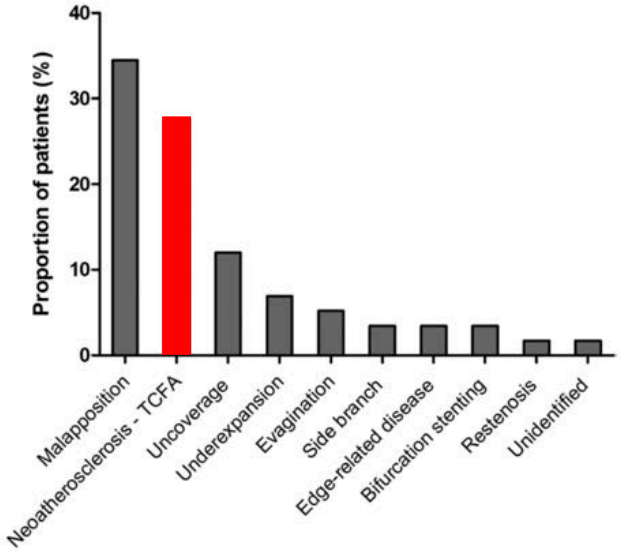
Mechanisms of Very Late Drug-Eluting Stent Thrombosis Assessed by Optical Coherence Tomography

58 thromboses très tardives

38 DES 1ère génération, 20 DES 2ème génération

Causes de thromboses :

- Malapposition 33%
- **Rupture néoathérosclérose 26%**
- Non couverture 10%
- Sous expansion 5%



Taniwaki M, Circulation 2016

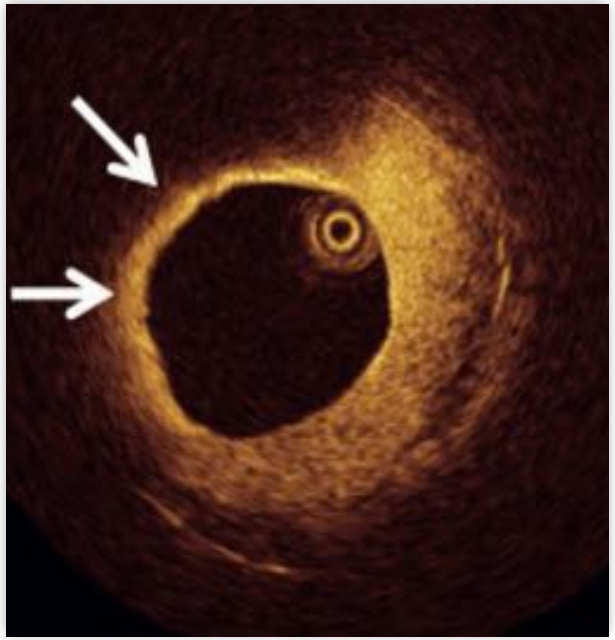
Néoathérosclérose

Resténose intrastent

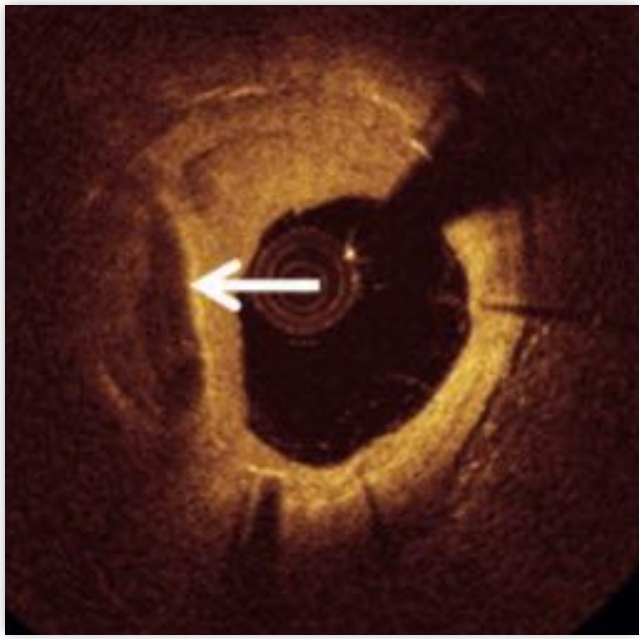
Analyse OCT de 152 stents avec > 50% resténose (128 DES, 24 BMS)

35,5% Néoathérosclérose

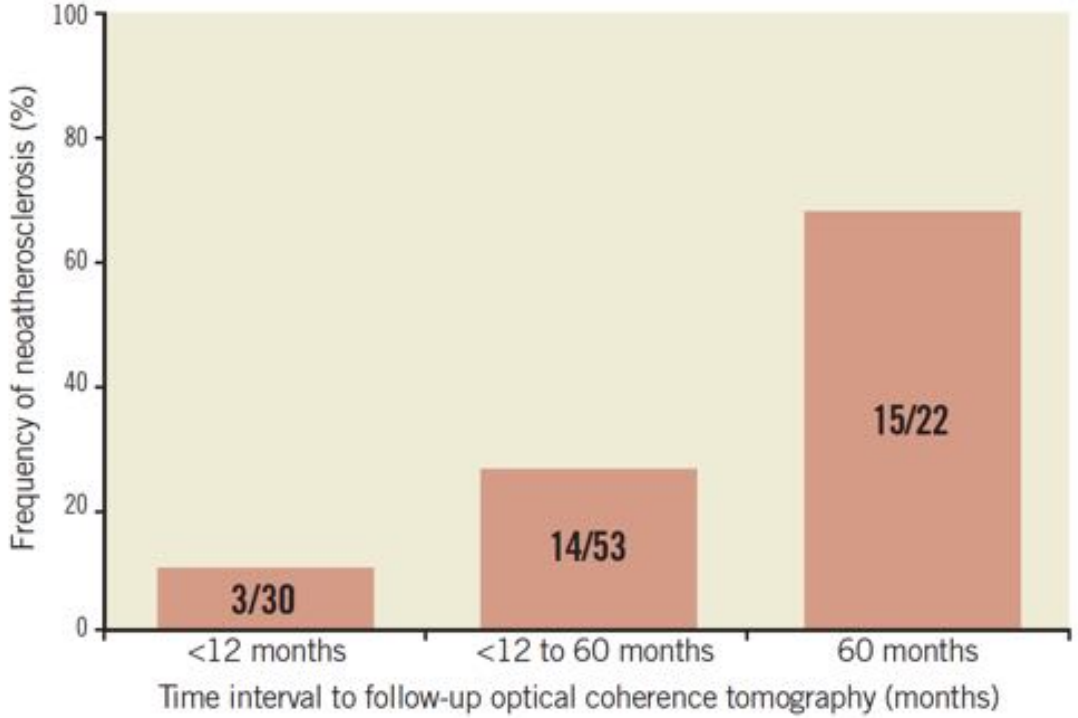
Délai resténoses : ***70 mois si NéoAth vs 13 mois*** *(58 mois DES / 129 mois BMS)*



Plaque lipidique



Plaque calcifiée

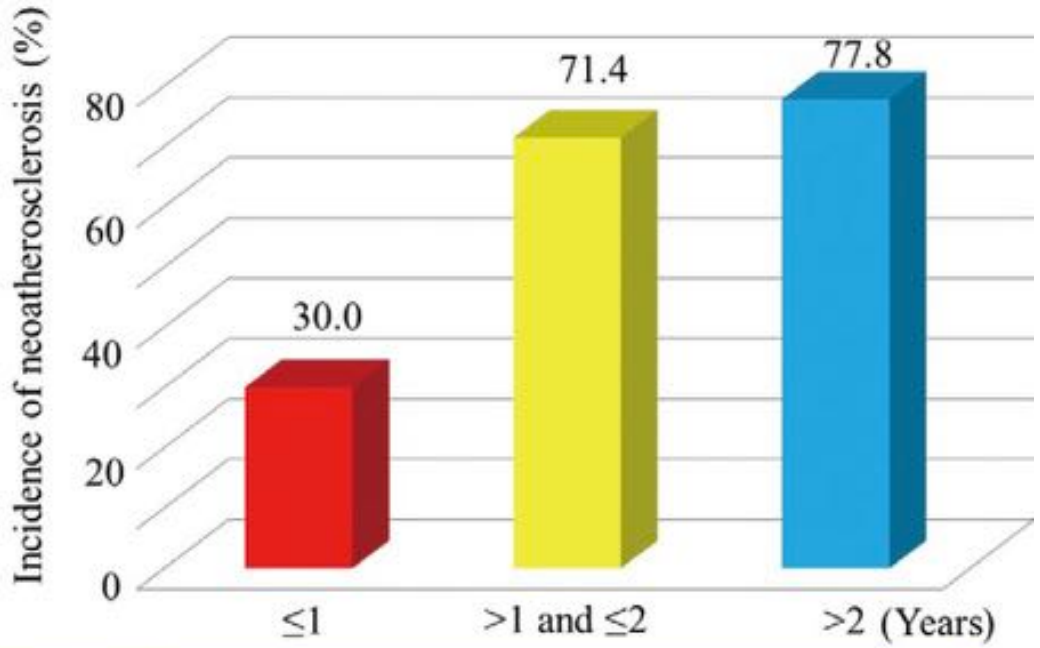


Lee SL, Eurointervention 2013

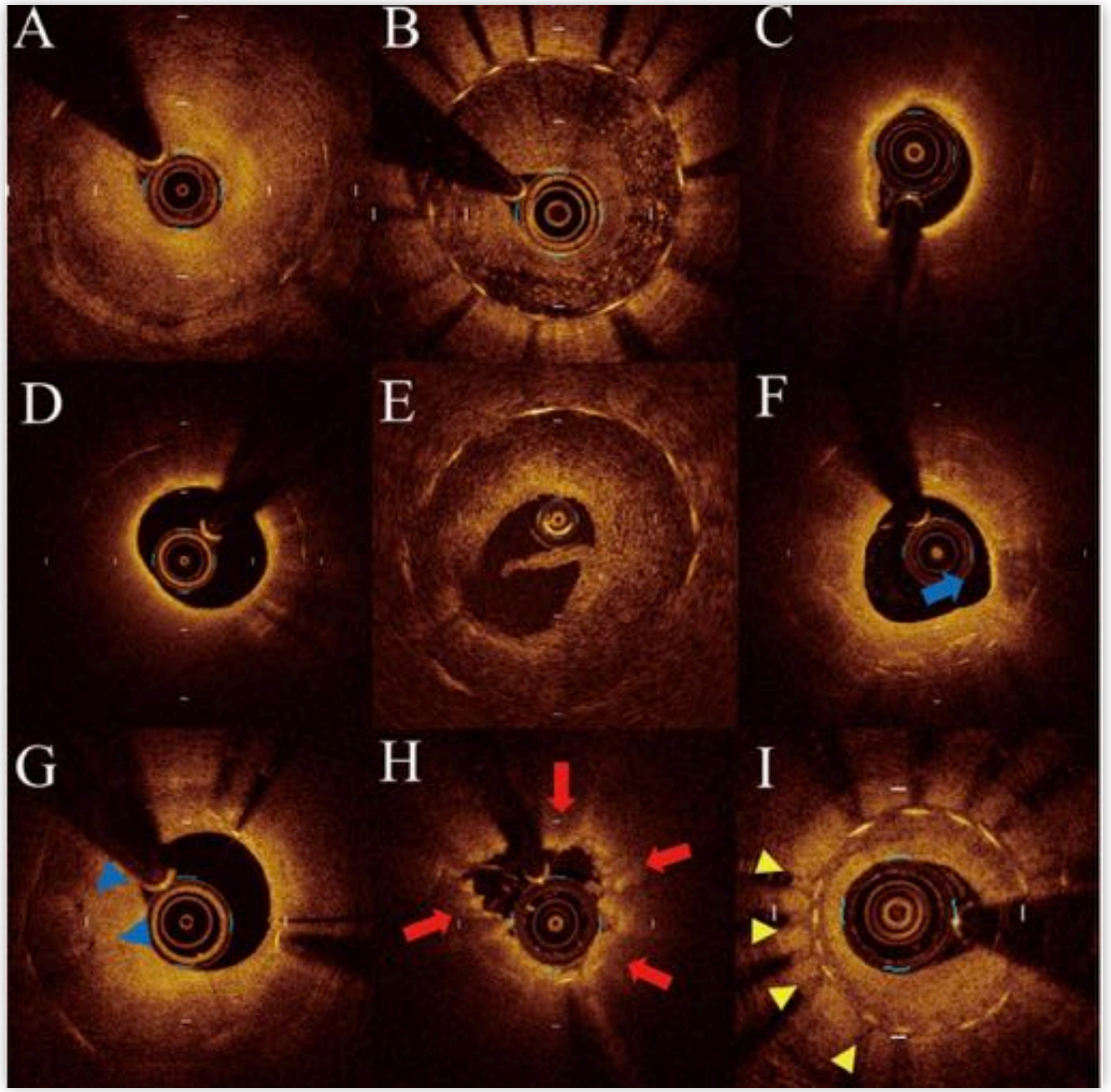
Néoathérosclérose

Resténose intrastent

53 resténoses intrastents
(DES de 2ème génération)

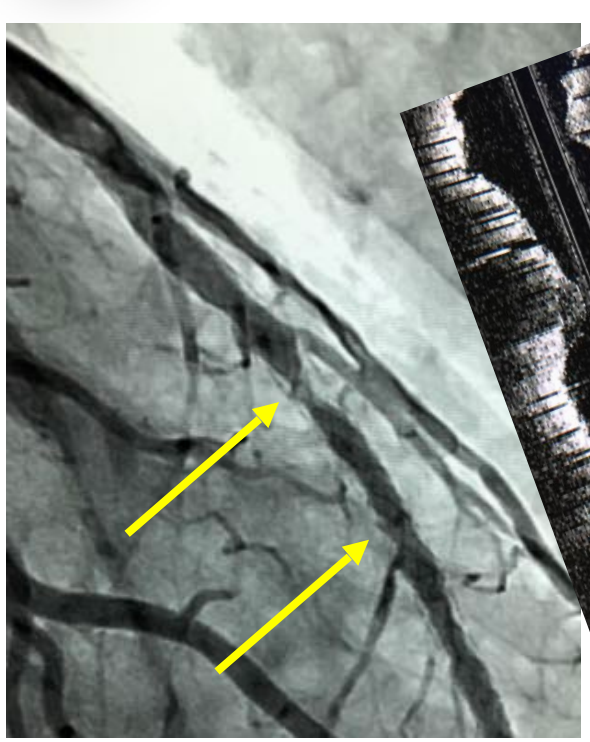


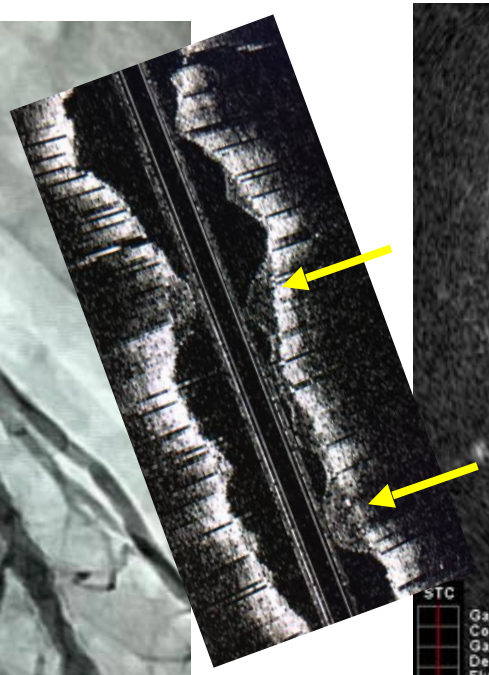
No. of lesions with neoatherosclerosis	9	10	7
No. of ISR lesions	30	14	9

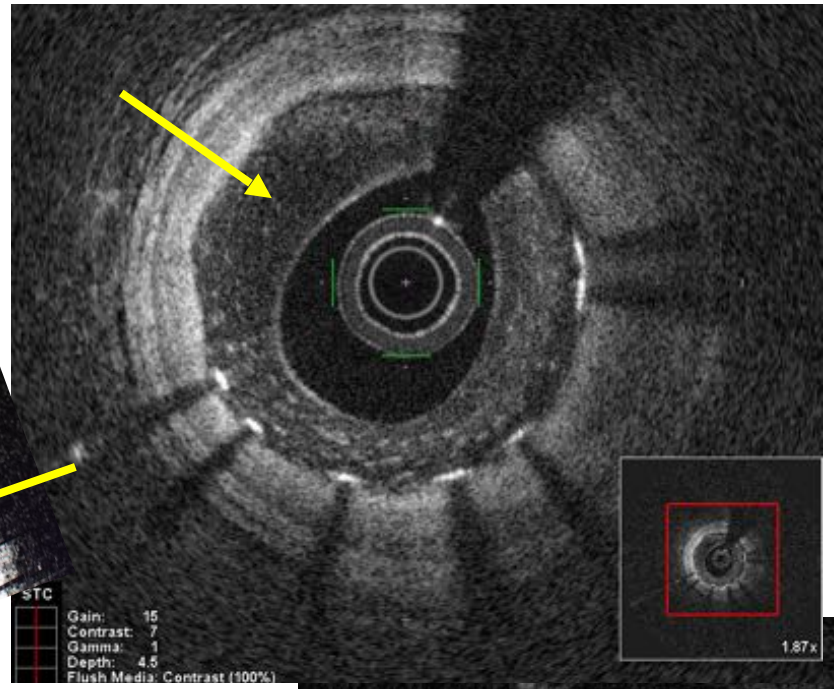


Jinnouchi H, Circ J 2017

Néoathérosclérose

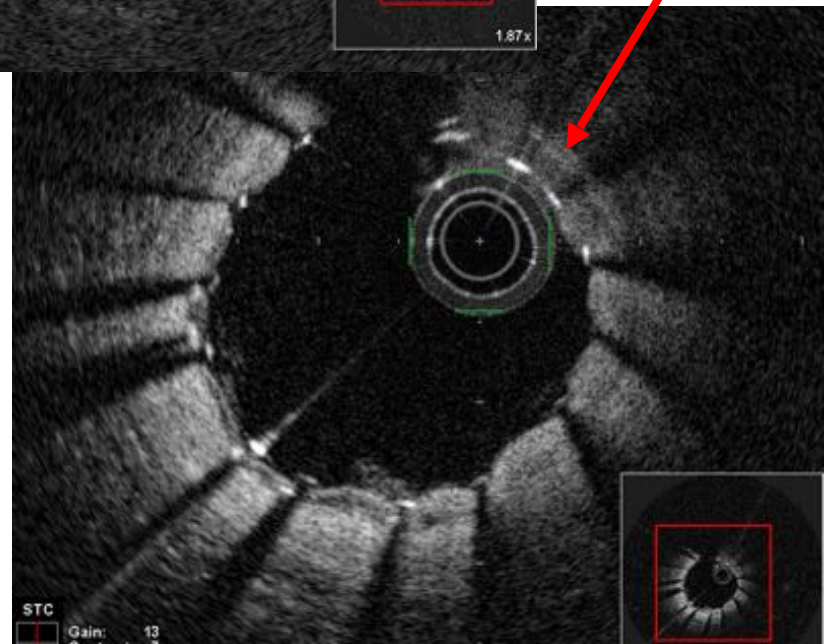




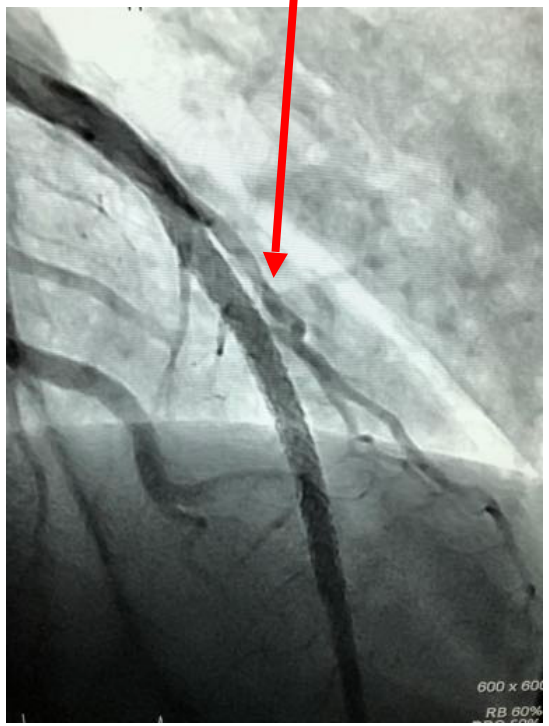


Resténose à J 100

DES 2ème génération (CTO IVA)



DES intra stent



Néoathérosclérose

Prise en charge

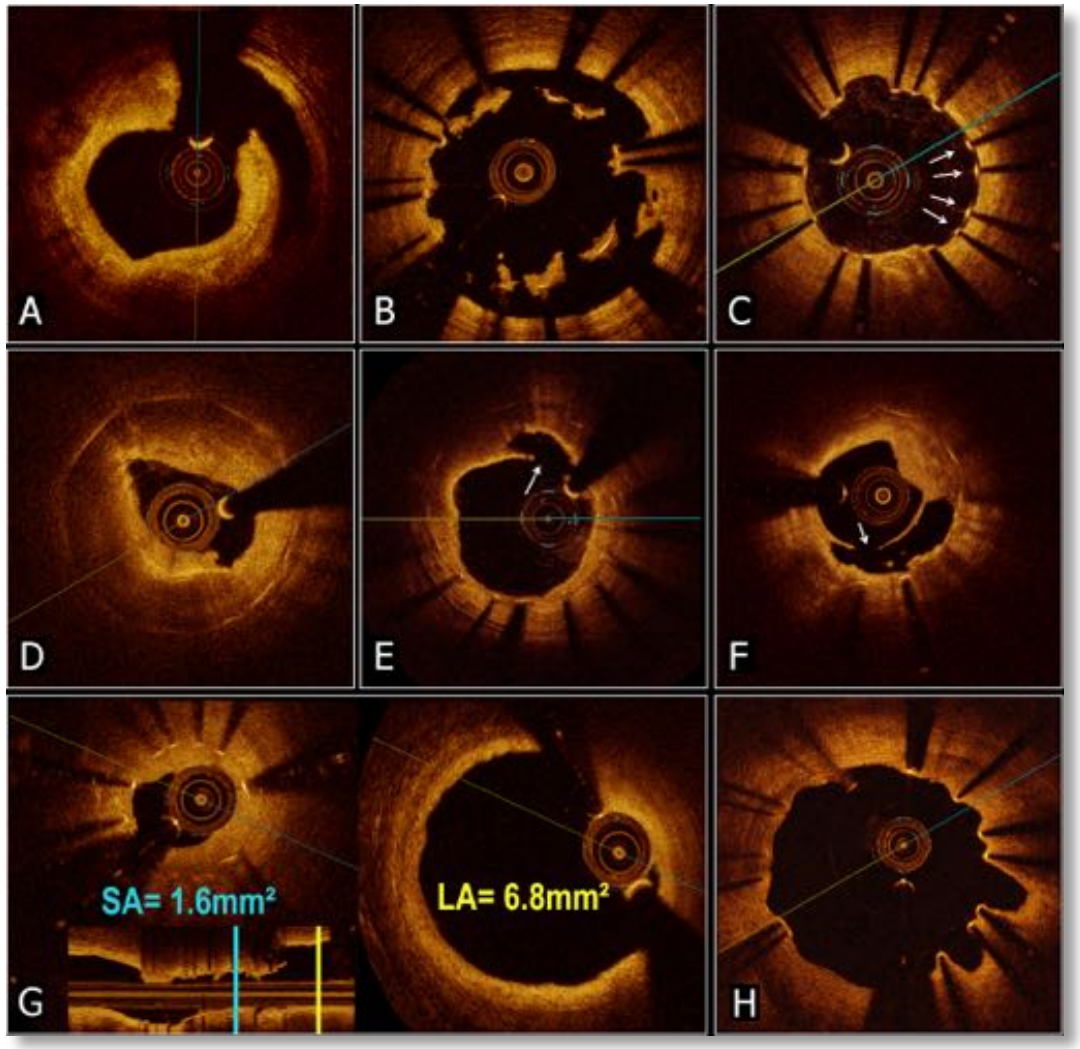
- SCA = Thrombose tardive

- **Confirmer la néoathérosclérose** et écarter diagnostics différentiels (malapposition, sous-déploiement)

- **Stent intra-stent** (DES dernière génération)

Néoathérosclérose

Prise en charge



PESTO

Mechanisms of Stent Thrombosis (n=120)

- *Malapposition 34%*
- ***Neoatherosclerosis 23%***

OCT influences management in 55% of ST cases

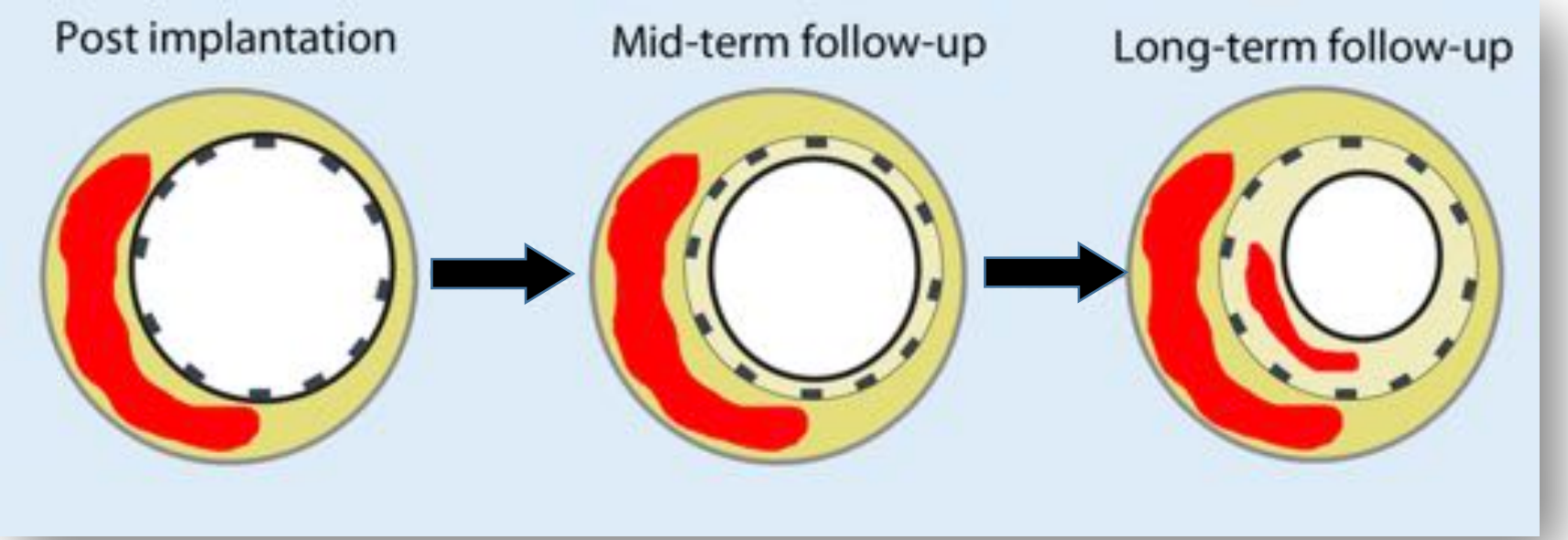
- *POBA 37%*
- *Medical therapy in 32%*
- ***Stenting 31%***

Souteyrand G, Eur Heart J 2016

Néoathérosclérose

Prise en charge

- Resténose intrastent



Confirmer la néoathérosclérose et écarter diagnostics différentiels (sous-déploiement)

Stent intra-stent (DES dernière génération) plutôt que Drug Coated Balloon ?

Néoathérosclérose

Treatment strategies for coronary in-stent restenosis: systematic review and hierarchical Bayesian network meta-analysis of 24 randomised trials and 4880 patients

In a network meta-analysis, contemporary treatment strategies for coronary in-stent restenosis (drug coated balloons and drug eluting stents) were compared with other treatments investigated over the years

Pooled evidence suggested comparable clinical and angiographic antirestenotic efficacy for drug coated balloons and drug eluting stents; plain balloons, bare metal stents, brachytherapy, rotational atherectomy, and cutting balloons were associated with an increased risk of target lesion revascularisation and inferior angiographic results

No differences in death, myocardial infarction, and stent thrombosis were noted across all the treatments investigated

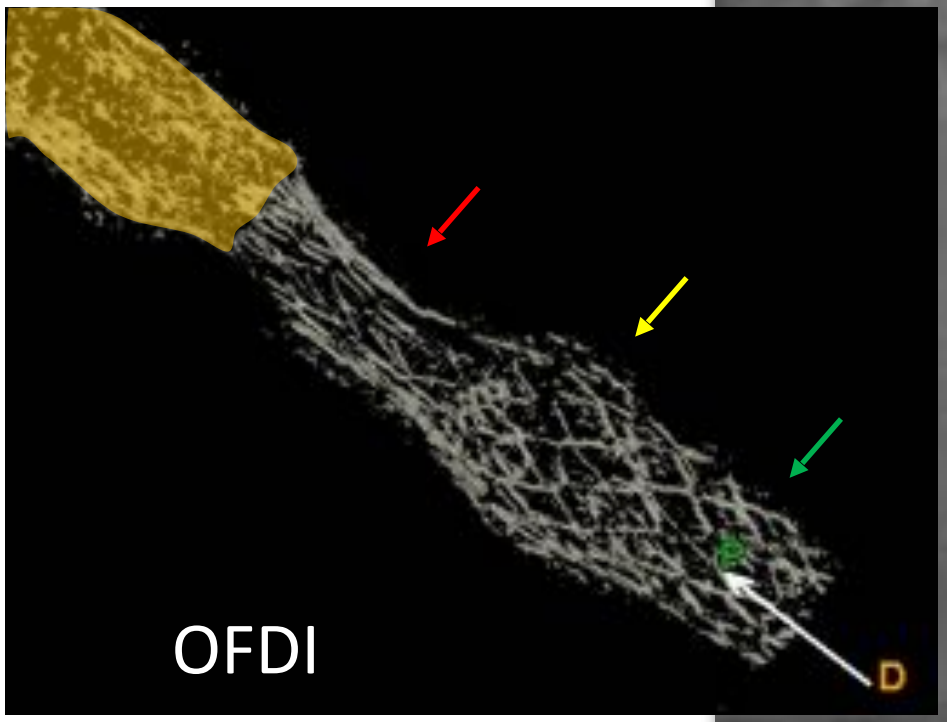
Giacoppo C, BMJ 2015

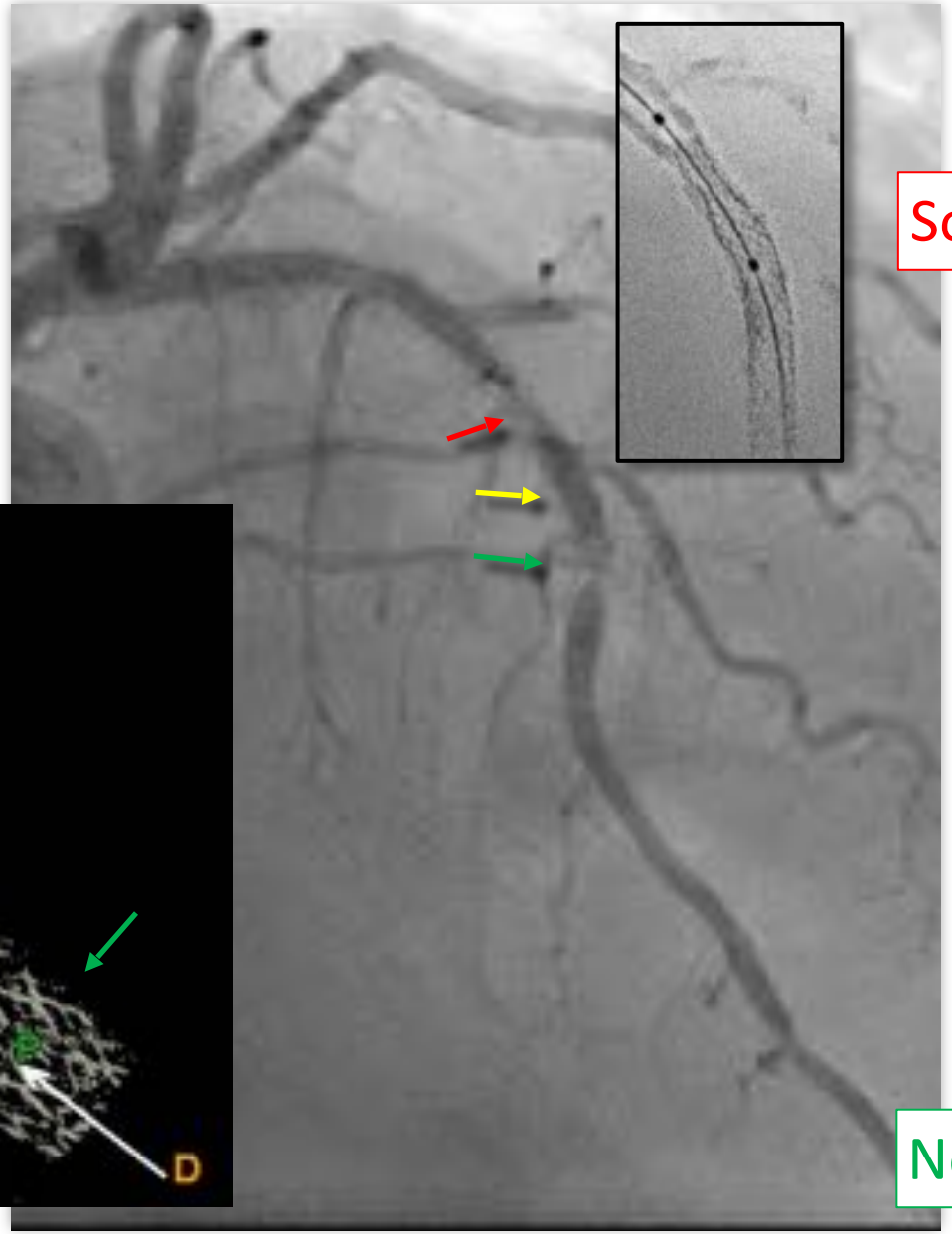
Néoathérosclérose

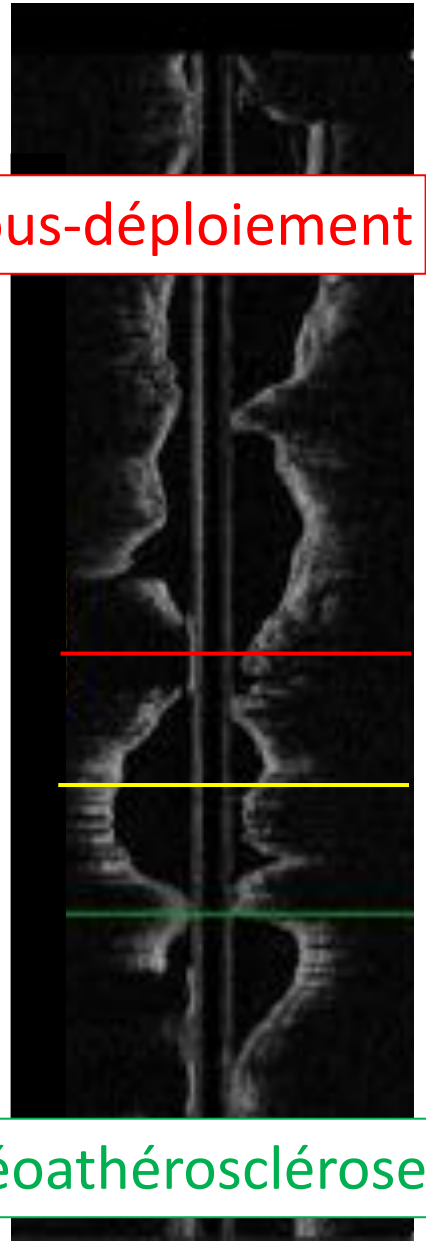
Me M., 64 ans

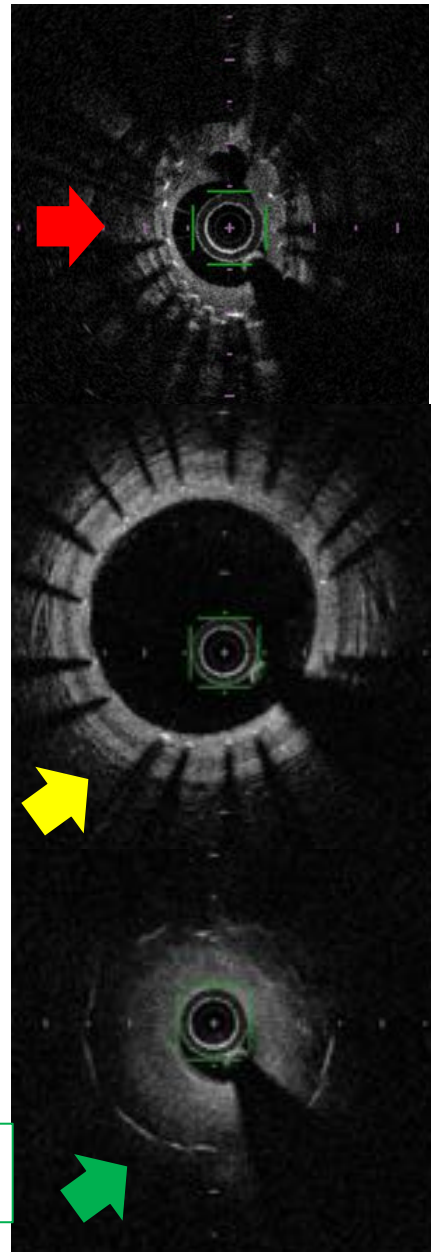
NSTEMI 4 ans après

DES IVA 3.0x26mm





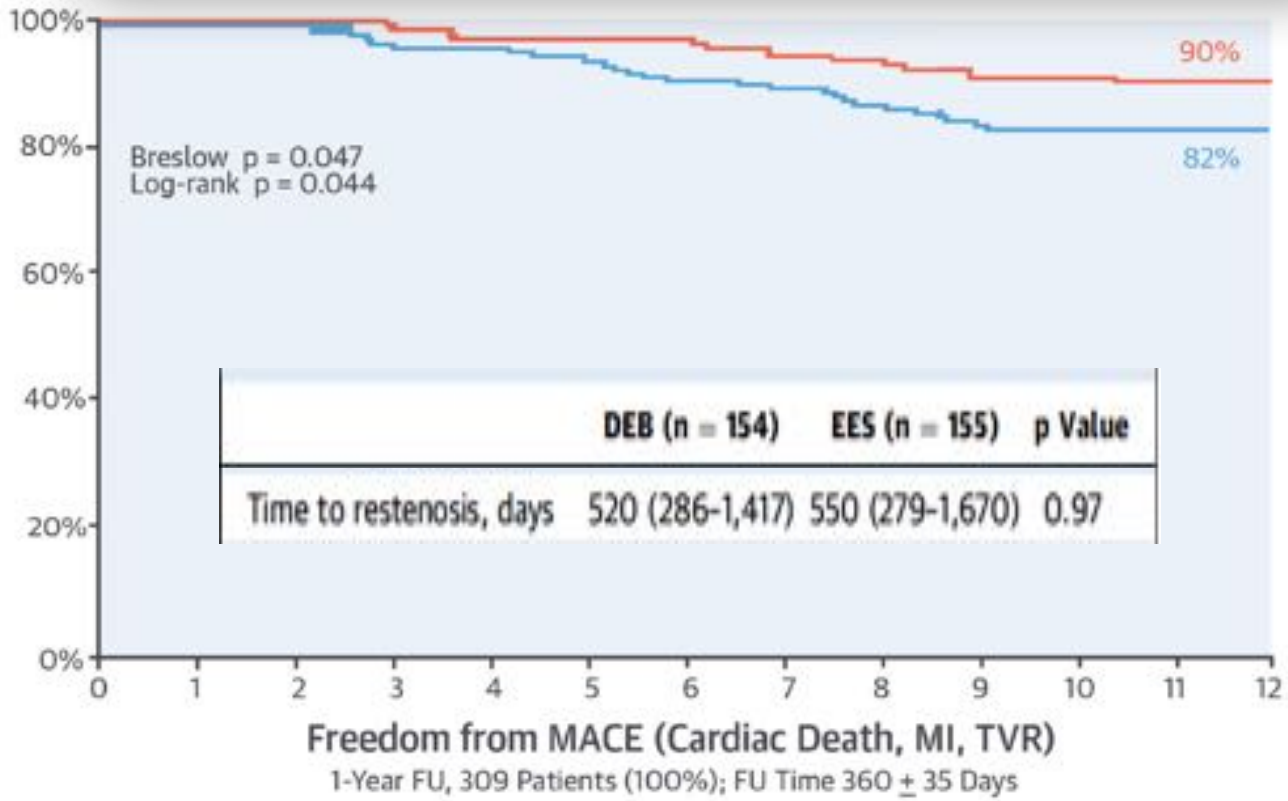




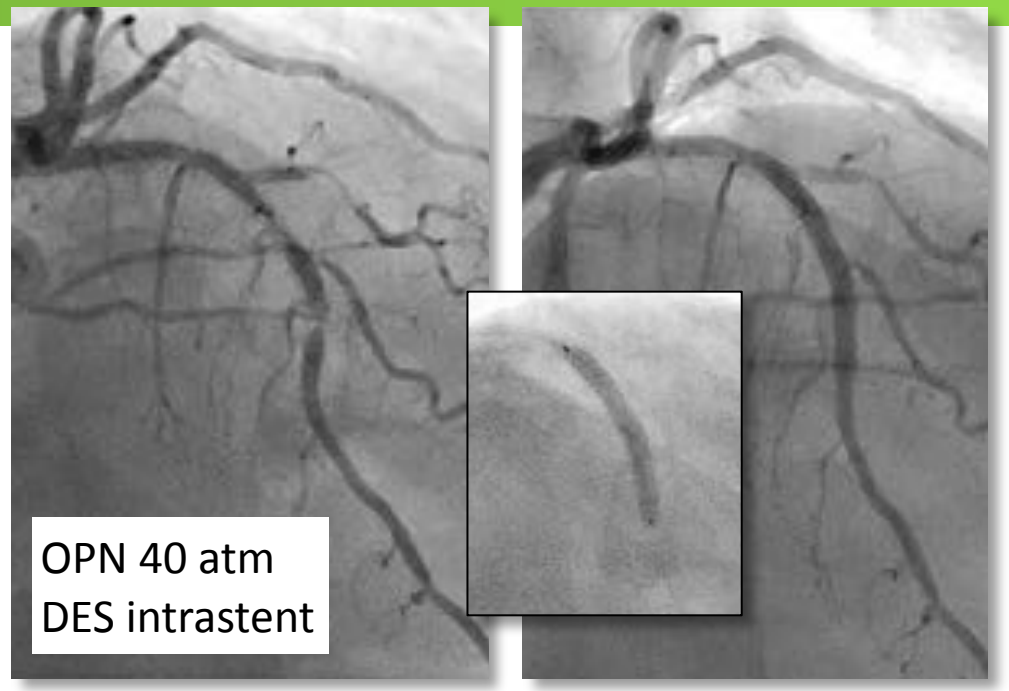
Néoathérosclérose

A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents

The RIBS IV Randomized Clinical Trial



	DEB (n = 154)	EES (n = 155)	p Value
Time to restenosis, days	520 (286-1,417)	550 (279-1,670)	0.97



CONCLUSIONS

This study demonstrated the superior efficacy of EES compared with DEB in patients with DES-ISR. Our findings strongly suggest that EES should be considered the therapy of choice in this vexing and challenging anatomic scenario.

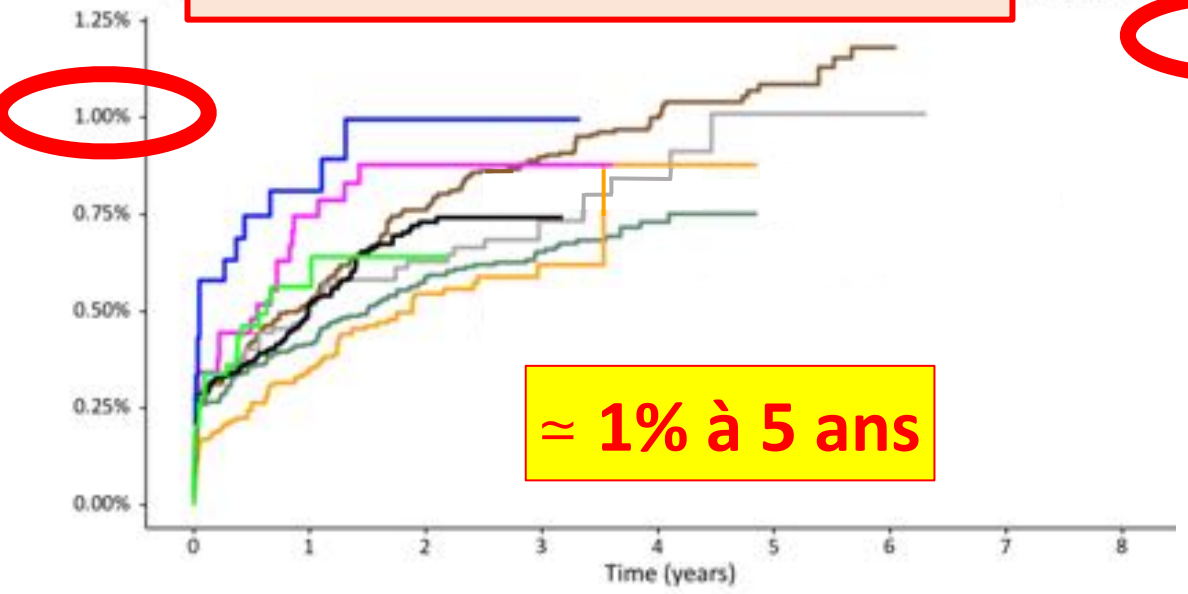
Alfonso F, J Am Coll Cardiol 2015

Néoathérosclérose

n°	Heure	Destination	Particularités	Voie
TGV	5111	10h37	MARSEILLE ST CHARLES	Retard probable:2h30
TGV	6607	10h54	LYON PERRACHE	Retard probable:2h30
TGV	5113	11h37	MONTPELLIER ST ROCH	Retard probable:2h30
TGV	6609	12h00	LYON PERRACHE	Retard probable:1h15
TGV	5313	12h07	MARSEILLE ST CHARLES	Retard probable:1h00
TGV	5311	12h11	MONTPELLIER ST ROCH	Retard probable:1h00
TGV	5317	12h37	MARSEILLE ST CHARLES	Retard probable:40mn
	16842	12h39	TOURS	Retard probable:30mn
TGV	6611	12h54	LYON PERRACHE	TRAIN A L'HEURE

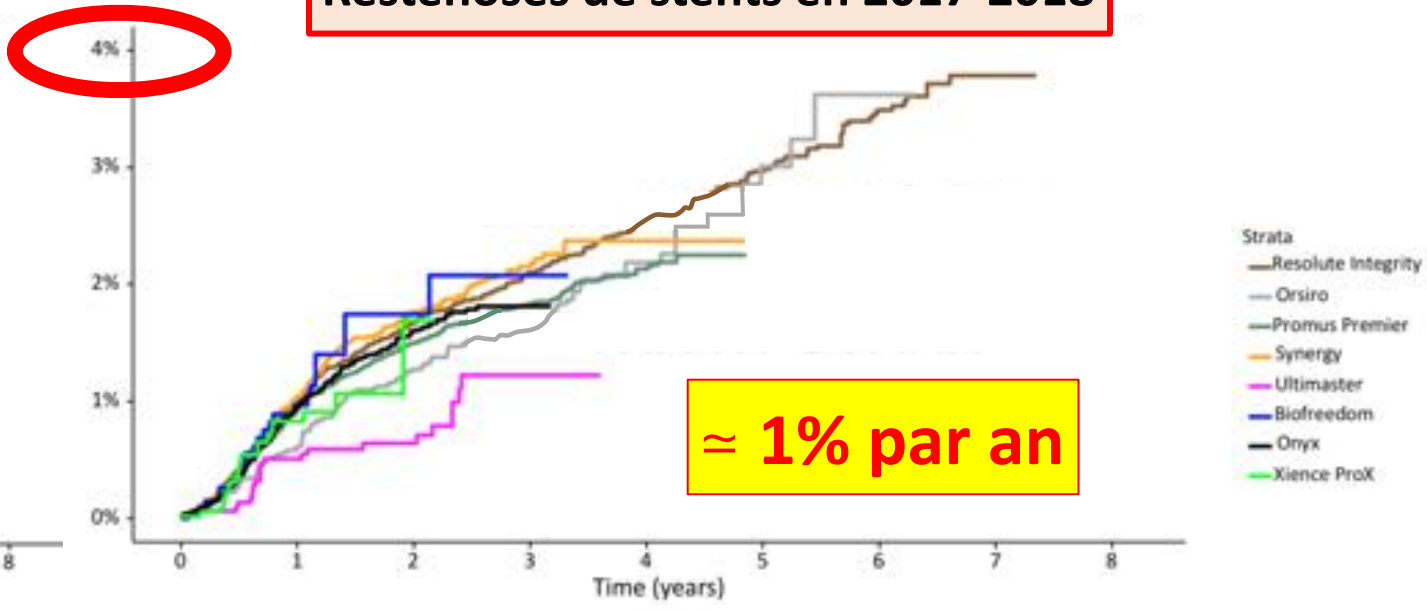
Excellents résultats des DES de 2ème génération **Registre SCAAR**

Thromboses de stents en 2017-2018



≃ 1% à 5 ans

Resténoses de stents en 2017-2018



≃ 1% par an

Conclusions

Néoathérosclérose

- Pathologie émergente
- **<u>Complications tardives des stents actifs</u>** (resténose, thrombose)
- Risque individuel faible mais…
- Prise en charge semblable lésion de novo, guidée par imagerie