Thrombosis Research 178 (2019) 12–16

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Neoatherosclerosis – From basic concept to clinical implication☆

Israel Mazin[a], Gideon Paul[b], Elad Asher[c,*]

[a] Heart Institute, Sheba Medical Center, Tel-Aviv University, Israel
[b] Heart Institute, Assuta Medical Center, Ben-Gurion University, Israel
[c] Heart Institute, Shaare Zedek Medical Center, Hebrew University, Jerusalem, Israel

ABSTRACT

Chronic inflammation within the coronary arteries with infiltration of macrophages into the endothelium results in atherosclerosis. Percutaneous coronary intervention (PCI) remains the standard of care for the treatment of most cases of atherosclerotic coronary artery disease (CAD). Intracoronary stents, either bare metal (BMS) or drug eluting (DES), can successfully treat luminal stenoses within the coronary arteries. Following successful PCI however, neointimal proliferation can develop within the deployed stent. Similar to the pathophysiology of native vessel atherosclerosis there is chronic inflammation within the neointima with infiltration of macrophages, a process called neoatherosclerosis, and can result in in-stent restenosis (ISR) and even acute thrombotic, coronary arterial occlusion following disruption of the neoatheroma. Neoatherosclerosis is a heterogeneous, pathobiological complication of PCI that can present more with angina recurrence or in its most extreme form with an acute coronary syndrome (ACS) In this review article, we will discuss possible mechanisms, clinical challenges, and the future therapies of neoatherosclerosis.

1. Introduction

Percutaneous coronary intervention (PCI) is considered to be the most common procedure in the field of cardiology [1]. In 1977 Andres Gruntzig performed the first case of balloon angioplasty; since then there has been a continuous evolution and improvement in the design and performance of catheters, balloons and stents. The first bare metal stents (BMS) were limited by an increased risk of stent thrombosis (ST) and target lesion revascularization (TLR) and were gradually replacement by the drug eluting stent (DES) with thinner struts and anti-proliferative drug coatings, which has reduced the occurrence of neointimal proliferation and the rates of TLR. Furthermore they have significantly reduced the incidence of ISR (20–30% in BMS to < 10% in DES) [2]. Recent concerns regarding late ST (30–60 days) and very late ST (> 1 year) have emerged in both BMS and DES. The cause of ST in either stent is thought to result from either strut mal-apposition, neoatherosclerosis, uncovered struts or stent under-expansion [3]. Adriaenssens et al. [4] reviewed more the 200 patients presenting with ST and concluded that both uncovered struts and under-expanded stents were the most common finding in acute or subacute ST, while uncovered struts and neoatherosclerosis were common in late and very late ST. Lastly, as opposed to native vessel atherosclerosis, which can take several decades to develop, tissue histology obtained from post mortem and DES studies indicate that additional cholesterol deposition may occur within a few months, and neoatherosclerosis may be present in the majority of restenotic lesions within DES. The aim of this paper is to review the current literature regarding the mechanism, pathophysiology and diagnosis of neoatherosclerosis, which remains poorly understood by many cardiologists and physicians, despite having been described in the literature for several years (Table 1).

2. Definition

Neoatherosclerosis is defined as the transformation within a stent from the normal intimal layer to an atherogenic neointima. The process is mediated by the accumulation of lipid-laden macrophages with or without calcification [5]. The development of a neointima ranges from months to years after stent deployment (depending on the stent type) in contrast to atherosclerosis within native coronary arteries, which requires a considerably longer time frame (decades) to develop [6] (Table 2).

3. Pathophysiology

Early pathological reports of neoatherosclerosis documented the accumulation of foamy macrophages adjacent to the luminal surface of

Abbreviations: PCI, percutaneous coronary intervention; BMS, bare-metal stent; DES, drug-eluting stent; TLR, target lesion revascularization; ST, stent thrombosis; TCFA, thin-cap fibrous atheroma; AMI, acute myocardial infarction; OCT, optical coherence tomography; IVUS, intravascular ultrasound; ISR, In-stent restenosis; VLST, very late stent thrombosis; MACE, major advance cardiovascular events; CKD, chronic kidney disease; ACS, acute coronary syndrome; STEMI, ST elevation myocardial infarction

☆ The authors declare that there is no conflict of interest regarding the publication of this paper.

* Corresponding author at: Shaare Zedek Medical Center, Jerusalem, Israel.
E-mail address: easher@szmc.org.il (E. Asher).

https://doi.org/10.1016/j.thromres.2019.03.016
Received 29 July 2018; Received in revised form 22 March 2019; Accepted 22 March 2019
Available online 23 March 2019
0049-3848/

Table 1
Atherosclerosis vs. neo-atherosclerosis.

	Atherosclerosis	Neo-atherosclerosis
Time	Decades	Months to a few years
Fatty streaks	Non-progressive	Progressive
Intimal thickening	Progressive	Rare
Necrotic core localization	Deep	Superficial with or without TCFA

Table 2
Neoatherosclerosis according to stent type.

Stent	BMS	1st generation DES	2nd generation DES
Thickness of strut	Thick	Thick	Thin
Polymer	None	Durable	Durable
Drug released	None	Paclitaxel or rapamycin derivates	Rapamycin derivates
Onset of neoatherosclerosis	± 900 days	SES ± 70 days PES ± 120 days	CoCr EES ± 270 days
Neoatherosclerosis process	Foreign-body inflammation	Accelerated atherosclerosis	
Necrotic core formation	± 900 days	± 300 days	
Calcification	−/+	SES + PES + + +	CoCr EES +
TCFA and in-stent plaque rapture	5 year	< 2 year	4 years

the stent and without communication with the original atherosclerosis tissue [7]. Thereafter, macrophage cells subsequently form a fibroatheromatous plaque, which can evolve to thin-cap fibrous atheroma (TCFA) with the risk of plaque rupture leading to myocardial infarction [8] (Fig. 1). Occasionally calcification can be seen in long-standing BMS and DES. The calcification process, which is commonly seen within the paclitaxel-eluting stent, is associated with persistent fibrin deposition within stent struts [7]. In general, the process of in-stent neoatherosclerosis presents as macrophage infiltration and apoptosis and results in the formation of a necrotic core [9].

The exact cause of this accelerated process is unknown, although several mechanisms have been proposed, including incomplete endothelial coverage resulting in endothelial dysfunction [9]. This inability to maintain a fully functional, competent endothelium is depicted by poorly formed cell junctions, reduced expression of antithrombotic molecules, and decreased production of nitric oxide, mainly after DES implantation [6]. This ineffective barrier permits the penetration of high levels of lipoprotein and proteoglycans into the subendothelial space, the initial stage of the neoatherosclerosis process [10].

Nakazawa et al. [11] described the early manifestations of neoatherosclerosis in different DES and BMS (209 vs 197 lesions respectively). The early sign of foamy macrophages cells was observed at 70 to 120 days in differing types of DES (sirolimus-eluting and paclitaxel-eluting stents), while in BMS it was noted at a later time point at approximately 900 days.

Furthermore, the necrotic core was observed between 270 and 360 days within DES as compared with 900 days in BMS. TCFA and in-stent plaque rapture (signs of unstable neoatherosclerosis) were observed less than two years after implantation of DES (first generation) compared to five years in BMS.

4. Clinical epidemiology

Early report by Chen et al. [12] stated the significant burden of in-stent restenosis after BMS implantation and speculated that the cause was neointimal proliferation. The majority of these patients presented with unstable or exertional angina (90%), as opposed to acute myocardial infraction (AMI). Takano et al. [13] used optical coherence tomography (OCT) to describe the neointima in patients after BMS implantation (Fig. 2). OCT was performed in twenty patients within six months after BMS implantation and after five years in 21 patients after BMS intervention. The appearance of intra-intima neovascularization in the latter group was significantly more prominent compared with the former group (62% vs. 0%, respectively; $p < 0.01$). Furthermore, patients with lipid-laden cells at the intima had higher incidence of in-stent restenosis, requiring a higher incidence of TLR. Ali et al. [14] have used both OCT and intravascular ultrasound (with infrared spectrometry) to assess the neointimal components of ISR in both DES and BMS. A total 65 patients (BMS, 14; DES 51) with anginal symptoms and signs of in-stent restenosis, as demonstrated by coronary angiography were included. Signs of neoatherosclerosis were observed in 36% of BMS implanted patients compere with 68% of DES implanted patients ($p = 0.02$) [14].

Nakazawa et al. [11], compared 142 patients with BMS to 157 with DES. They found that the incidence of neoatherosclerosis was greater in the DES group compared with the BMS group (31% vs 16%, $p < 0.001$ respectively). The median time of any neoatherosclerosis signs in BMS was 2160 days (IQR: 1800–2880) while signs of neoatherosclerosis in the DES groups were observed at a median time of 420 days (IQR: 361–683). Almost the same results were seen in an additional study [14], where neoatherosclerosis developed at a median time point of 111 days in the DES group as compared with 295 days in the BMS group. A different mechanism was postulated to cause neoatherosclerosis between the different stent types. Autopsies from patients who underwent PCI with BMS [15] demonstrated a prominent infiltration of lipid-laden macrophages with dense collagen-degrading matrix metalloproteinase activity expressed WITHIN ruptured and vulnerable plaques. This process occurs more rapidly in patients treated with DES, mainly due to the prevention of endothelial cell proliferation, viability, and migration, which allows infiltration of lipid-laden foamy macrophage into the vessel, thereby accelerating atherosclerosis [16–19].

A Recent OCT based report by Joner et al. [20] has shown that in patients presenting with very-late ST, neoatherosclerosis was the most common cause for very late ST with a prevalence of 58/134 (43.3%). The median time from the initial event to the onset of the very late ST was 5.95 years (IQR: 2.99 to 8.65 years), with a median time of ST for DES and BMS ranging from 4.52 years (IQR: 2.1 to 6.5 years) and 8.24 years (IQR: 5.0to 11.49 years) respectively, ($p < 0.0001$). Furthermore, while examining OCT images, macrophage infiltration was more frequent in patients with plaque rupture compared with those without (50.2% vs. 22.2%; $p < 0.0001$), whereas calcification was more often observed in frames without plaque rupture (17.2% vs. 4%; $p < 0.0001$). As in previous studies, DES was also associated with an increased risk of neoatherosclerosis (HR 2.2 95% CI: 1.15–4.3, $p = 0.02$).

5. Diagnosis and clinical relevance

The diagnosis of neoatherosclerosis can be made at autopsy or through advanced coronary artery imaging. Earlier reports were able to measure the luminal diameter by angiography and then speculate the cause of late ISR [21]. This was thought to be the result of neointimal hyperplasia. The average rate of restenosis was reported to be approximately 30% at three-year follow-up with associated mortality and MACE rates of 9.2% and 25.4% respectively. Subsequent four year data was published in 2002, in which a total 405 patients with 424 lesions underwent PCI with Palmaz–Schatz BMS [22]. Restenosis rates were also 30% > 4-year after BMS implantation and the majority had a reduction in luminal diameter by > 50%. Nevertheless, only 11% of the lesions required PCI due to late ISR (> 70% reduction in lumen diameter). Inoue et al. [15] performed 19 autopsy studies following a

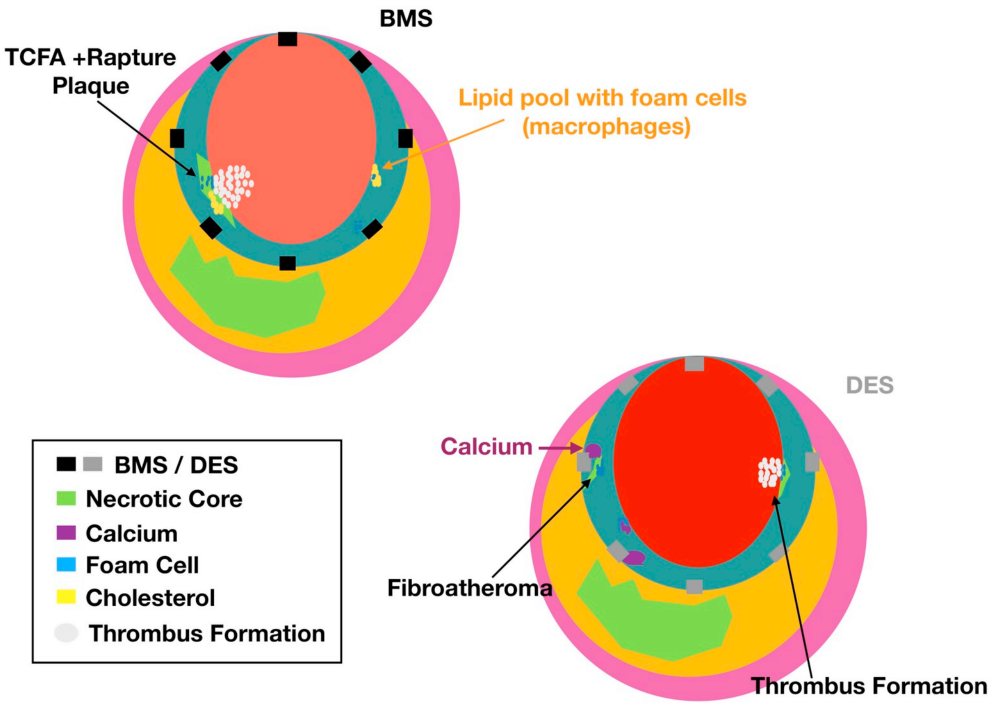
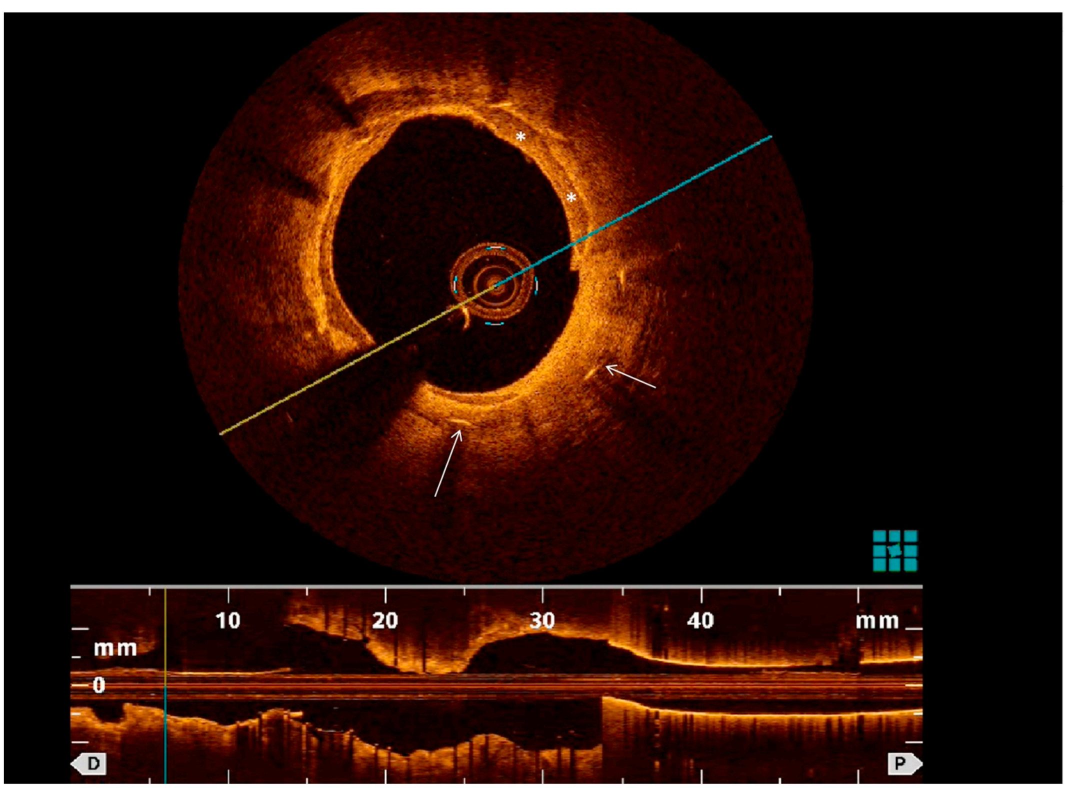


Fig. 1. Process in atherosclerosis and neoatherosclerosis, and in DES vs. BMS (DES- Drug eluting stent; BMS-Bare metal stent).



Asterisks – neoatherosclerosis; Arrows – Stent struts

Fig. 2. Optical coherence tomography showing neoatherosclerosis.

diagnosis of non-cardiac death occurring between two to seven years post PCI with Palmaz–Schatz BMS. Their results confirmed that stainless steel stents evoked a peri-strut persistent, inflammatory response, with subsequent new indolent atherosclerotic changes and consequent increased plaque vulnerability as previously discussed.

6. Coronary imaging

Current guidelines recommend intravascular ultrasound (IVUS) or optical coherence tomography (OCT) to assess the mechanisms of stent failure [23,24]. However, the resolution of OCT (10–20 μm) compared to that of IVUS (80–120 μm), makes it the preferred intracoronary imaging modality to evaluate neointimal tissue within the stented segment. OCT can provide detailed information regarding the composition of restenosic tissue (tissue structure, backscatter and micro vessels) [3,13,25,26].

Takano et al. [13], assessed 21 lesions in patients who underwent PCI with BMS stents. Five years post PCI, the majority (67%) of stents showed lipid-laden intimal macrophages and 38% of them had evidence of thrombus formation. The mean TCFA diameter was between 80 ± 59 μm, and was related to an increase in the incidence of ACS. Kang et al. [27] have acquired information by using OCT and IVUS (virtual histology) from 50 patients who were diagnosed with in-stent restenosis (defined as diameter stenosis > 50% by visual estimation at follow-up angiography). Twenty patients presented with unstable angina and thirty with stable angina. Fifty percent of the lesions were treated with Cypher® DES, 20% with Taxus®, 6% with Endeavor®, 4% with Xience® with remaining lesions treated with other types of stents. The median follow-up time was 32.2 months (IQR 9.2 to 52.3). Of a total 50 lesions, 19 lesions had two overlapping DES and four lesions had three overlapping DES. Lipid neointima was diagnosed in 90% (45 lesions) by OCT, while the rest showed evidence of calcification. Compared with stable patients, unstable patients had thinner TCFA (55 vs 100 μm, $p = 0.006$) and an increased incidence of thrombi (80% vs 43%, $p = 0.01$). Overall, 26 lesions (52%) had at least one site of in-stent TCFA-containing neointima; and 29 (58%) had at least one site of in-stent neointimal rupture. Compared with OCT, IVUS imaging demonstrated only ten (34%) cases of IVUS-defined neointimal rupture. Hence, many believe that OCT is the current gold standard imaging modality to best define neointimal rupture.

Another study compared the use of OCT in 151 patients with (n = 77) and without (n = 74) evidence of neoatherosclerosis. Within the former group, the time taken to develop neoatherosclerosis after stent implantation was on average 69 months in BMS-treated patients as compared to 26 months treated with DES [28]. Furthermore, the frequency of lipid-laden neointima was significantly higher in the DES group compared with the BMS group (56.6% versus 32.9%, $p = 0.002$, respectively). Multivariate analysis for the prediction of neoatherosclerosis concluded that stent age > 48 months, all subtypes of DES, current smoking, chronic kidney disease (CKD) and the use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, were independent predictors for the development of neoatherosclerosis.

An additional multicenter analysis reported that in first and second generation DES, the prevalence of neoatherosclerosis using OCT intracoronary imaging was 27.4% (58/212) [29]. First generation DES compared to second-generation stents showed higher rate of neoatherosclerosis (45.5% vs 10.8%, $p < 0.001$). There was no difference between the different types of stents. Furthermore, patients with neoatherosclerosis were at higher risk for ACS (19.0% vs. 3.9%, $p = 0.001$). A multivariable analysis for the predication of neoatherosclerosis found that CKD, low-density lipoprotein (LDL) level of > 70 mg/dl and stent age were independent predictors for neoatherosclerosis.

Recently, Kuroda et al. [30] published their long-term follow-up of 175 patients who underwent coronary angiography with OCT imaging during 2005 to 2013. The presence of neoatherosclerosis was independently associated with an increased risk of cardiac death, TLR and very late stent thrombosis. Kim et al. [31] have reinforced this phenomena that neoatherosclerosis is associated with higher rates of TLR (9% vs 55%, respectively; $p < 0.001$) while patients tend to be more symptomatic (13% vs 57%, $p < 0.001$) as compared to those without signs of neoatherosclerosis.

Joner et al. [20] have published the recent European experience (PRESTIGE Consortium) in patients presenting with VLST. OCT was performed within a total of 134 lesions in 134 patients, of which 58 were diagnosed with neoatherosclerosis. All patients with neoatherosclerosis had presented with an ACS (77% secondary to STEMI). In patients with neoatherosclerosis, the main cause of thrombosis, occurring in 69% of cases, was in-stent plaque rupture. In a subsequent multivariate analysis DES, as opposed to BMS, was found to be a predicator of neoatherosclerosis. In addition, previous MI was associated with an increased risk of plaque rapture in patients presenting with neoatherosclerosis (HR 4.87 95% CI: 1.73–13.73, $p = 0.003$), other risk factors such as DES, diabetes, smoking or bifurcation lesions showed no associated increased risk. Nevertheless, given that intra-coronary imaging is not routinely performed and that many cardiologists are unfamiliar with the entity of neoathrosclerosis, some physicians might confuse late stent thrombosis from neoatherosclerosis with inadequate struts coverage or inadequate anti–platelet therapy or ISR.

7. Summary

Neoatherosclerosis is now recognized as a common complication of PCI with DES. Increasing use of intracoronary imaging, specifically OCT, will inevitably result in increased awareness and understanding. Neoatherosclerosis is not a benign process and can result in late and very late ST. The basic pathological mechanism involves the formation of do novo lipid-laden macrophages within the neointimal region. The appearance of neoatherosclerosis is a risk factor for higher rates of ACS, TLR and anginal symptoms. Several risk factors had been identified regarding an increased risk in the development of neoatherosclerosis namely, type of stent implanted, chronic renal failure, smoking and LDL levels. These factors may become the focus for future studies in order to reduce this phenomenon. Prospective cohort studies, advanced coronary imaging and maybe prolonged treatment with dual anti-platelet therapy, will be fundamental to further understand and treat this phenomena [32].

References

[1] Writing Group Members, D. Lloyd-Jones, R.J. Adams, T.M. Brown, M. Carnethon, S. Dai, G. De Simone, T.B. Ferguson, E. Ford, K. Furie, C. Gillespie, A. Go, K. Greenlund, N. Haase, S. Hailpern, P.M. Ho, V. Howard, B. Kissela, S. Kittner, D. Lackland, L. Lisabeth, A. Marelli, M.M. McDermott, J. Meigs, D. Mozaffarian, M. Mussolino, G. Nichol, V.L. Roger, W. Rosamond, R. Sacco, et al., Heart disease and stroke statistics—2010 update: a report from the American Heart Association, Circulation 121 (2010) e46–e215. American Heart Association, Inc..

[2] L. Mauri, T.S. Silbaugh, R.E. Wolf, K. Zelevinsky, A. Lovett, Z. Zhou, F.S. Resnic, S.-L.T. Normand, Long-term clinical outcomes after drug-eluting and bare-metal stenting in Massachusetts, Circulation 118 (2008) 1817–1827. American Heart Association, Inc..

[3] M. Taniwaki, M.D. Radu, S. Zaugg, N. Amabile, H.M. Garcia-Garcia, K. Yamaji, E. Jørgensen, H. Kelbæk, T. Pilgrim, C. Caussin, T. Zanchin, A. Veugeois, U. Abildgaard, P. Jüni, S. Cook, K.C. Koskinas, S. Windecker, L. Räber, Mechanisms of very late drug-eluting stent thrombosis assessed by optical coherence tomography, CLINICAL PERSPECTIVE. American Heart Association, Inc. 133 (2016) 650–660.

[4] T. Adriaenssens, M. Joner, T.C. Godschalk, N. Malik, F. Alfonso, E. Xhepa, D. De Cock, K. Komukai, T. Tada, J. Cuesta, V. Sirbu, L.J. Feldman, F.-J. Neumann, A.H. Goodall, T. Heestermans, I. Buysschaert, O. Hlinomaz, A. Belmans, W. Desmet, J.M. Berg ten, A.H. Gershlick, S. Massberg, A. Kastrati, G. Guagliumi, R.A. Byrne, Optical coherence tomography findings in patients with coronary stent thrombosis, 136 (2017) 1007–1021.

[5] H. Komiyama, Neoatherosclerosis: coronary stents seal atherosclerotic lesions but result in making a new problem of atherosclerosis, WJC 7 (2015) 776–779.

[6] M.E. Romero, K. Yahagi, F.D. Kolodgie, R. Virmani, Neoatherosclerosis from a pathologist's point of view, Arterioscler. Thromb. Vasc. Biol. 35 (2015) e43–e49.

[7] K. Yahagi, F.D. Kolodgie, F. Otsuka, A.V. Finn, H.R. Davis, M. Joner, R. Virmani, Pathophysiology of native coronary, vein graft, and in-stent atherosclerosis, Nat. Rev. Cardiol. 13 (2015) 79–98.

[8] F. Otsuka, R.A. Byrne, K. Yahagi, H. Mori, E. Ladich, D.R. Fowler, R. Kutys, E. Xhepa, A. Kastrati, R. Virmani, M. Joner, Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment, Eur. Heart J. 36 (2015) 2147–2159.

[9] R.A. Byrne, M. Joner, A. Kastrati, Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014, Eur. Heart J. 36 (2015) 3320–3331.

[10] A.P. Burke, F.D. Kolodgie, A. Farb, D.K. Weber, G.T. Malcom, J. Smialek, R. Virmani, Healed plaque ruptures and sudden coronary death: evidence that subclinical rupture has a role in plaque progression, Circulation 103 (2001) 934–940. American Heart Association, Inc..

[11] G. Nakazawa, F. Otsuka, M. Nakano, M. Vorpahl, S.K. Yazdani, E. Ladich,

F.D. Kolodgie, A.V. Finn, R. Virmani, The pathology of neoatherosclerosis in human coronary implants, J. Am. Coll. Cardiol. 57 (2011) 1314–1322 Elsevier Inc..

[12] M.S. Chen, J.M. John, D.P. Chew, D.S. Lee, S.G. Ellis, D.L. Bhatt, Bare metal stent restenosis is not a benign clinical entity, Am. Heart J. 151 (2006) 1260–1264.

[13] M. Takano, M. Yamamoto, S. Inami, D. Murakami, T. Ohba, Y. Seino, K. Mizuno, Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents, J. Am. Coll. Cardiol. 55 (2009) 26–32 Elsevier Inc..

[14] Z.A. Ali, T. Roleder, J. Narula, B.D. Mohanty, U. Baber, J.C. Kovacic, G.S. Mintz, F. Otsuka, S. Pan, R. Virmani, S.K. Sharma, P. Moreno, A.S. Kini, Increased thin-cap neoatheroma and periprocedural myocardial infarction in drug-eluting stent restenosis: multimodality intravascular imaging of drug-eluting and bare-metal stents, Circ. Cardiovasc. Interv. 6 (2013) 507–517. American Heart Association, Inc..

[15] K. Inoue, K. Abe, K. Ando, S. Shirai, K. Nishiyama, M. Nakanishi, T. Yamada, K. Sakai, Y. Nakagawa, N. Hamasaki, T. Kimura, M. Nobuyoshi, T.A. Miyamoto, Pathological analyses of long-term intracoronary Palmaz–Schatz stenting, Cardiovasc. Pathol. 13 (2004) 109–115.

[16] S.C. Moss, D.J. Lightell Jr., S.O. Marx, A.R. Marks, T.C. Woods, Rapamycin regulates endothelial cell migration through regulation of the cyclin-dependent kinase inhibitor p27 Kip1, J. Biol. Chem. 285 (2010) 11991–11997. American Society for Biochemistry and Molecular Biology.

[17] A. Barilli, R. Visigalli, R. Sala, G.C. Gazzola, A. Parolari, E. Tremoli, S. Bonomini, A. Simon, E.I. Closs, V. Dall'Asta, O. Bussolati, In human endothelial cells rapamycin causes mTORC2 inhibition and impairs cell viability and function, Cardiovasc. Res. 78 (2008) 563–571.

[18] P. Jiang, Y. Lan, J. Luo, Y.-L. Ren, D.-G. Liu, J.-X. Pang, J. Liu, J. Li, C. Wang, J.-P. Cai, Rapamycin promoted thrombosis and platelet adhesion to endothelial cells by inducing membrane remodeling, BMC Cell Biol. 15 (7) (2014).

[19] A. Habib, V. Karmali, R. Polavarapu, H. Akahori, Q. Cheng, K. Pachura, F.D. Kolodgie, A.V. Finn, Sirolimus-FKBP12.6 impairs endothelial barrier function through protein kinase C-α activation and disruption of the p120-vascular endothelial cadherin interaction, Arterioscler. Thromb. Vasc. Biol. 33 (2013) 2425–2431. American Heart Association, Inc..

[20] M. Joner, T. Koppara, R.A. Byrne, M.I. Castellanos, J. Lewerich, J. Novotny, ... A. Kastrati, Neoatherosclerosis in patients with coronary stent thrombosis: findings from optical coherence tomography imaging (a report of the PRESTIGE consortium), J. Am. Coll. Cardiol. Intv. 11 (14) (2018) 1340–1350.

[21] T. Kimura, Y. Nakagawa, T. Tamura, S. Kaburagi, Y. Sawada, Y. Sato, H. Yokoi, N. Hamasaki, H. Nosaka, Three-year follow-up after implantation of metallic coronary-artery stents, N. Engl. J. Med. 334 (1996) 561–566.

[22] T. Kimura, Long-term clinical and angiographic follow-up after coronary stent placement in native coronary arteries, 105 (2002) 2986–2991.

[23] Authors/Task Force Members, S. Windecker, P. Kolh, F. Alfonso, J.-P. Collet, J. Cremer, V. Falk, G. Filippatos, C. Hamm, S.J. Head, P. Jüni, A.P. Kappetein, A. Kastrati, J. Knuuti, U. Landmesser, G. Laufer, F.-J. Neumann, D.J. Richter, P. Schauerte, M. Sousa-Uva, G.G. Stefanini, D.P. Taggart, L. Torracca, M. Valgimigli, W. Wijns, A. Witkowski, 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), Eur. Heart J. (2014) 2541–2619.

[24] Writing Committee Members, G.N. Levine, E.R. Bates, J.C. Blankenship, S.R. Bailey, J.A. Bittl, B. Cercek, C.E. Chambers, S.G. Ellis, R.A. Guyton, S.M. Hollenberg, U.N. Khot, R.A. Lange, L. Mauri, R. Mehran, I.D. Moussa, D. Mukherjee, B.K. Nallamothu, H.H. Ting, 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions, Circulation 124 (2011) e574–e651. American Heart Association, Inc..

[25] S.-J. Lee, B.K. Kim, J.S. Kim, Y.G. Ko, D. Choi, Y. Jang, M.K. Hong, Evaluation of neointimal morphology of lesions with or without in-stent restenosis: an optical coherence tomography study, Clin. Cardiol. 34 (2011) 633–639 Wiley Periodicals, Inc..

[26] N. Gonzalo, P.W. Serruys, T. Okamura, H.M. van Beusekom, H.M. Garcia-Garcia, G. van Soest, W. van der Giessen, E. Regar, Optical coherence tomography patterns of stent restenosis, Am. Heart J. 158 (2009) 284–293.

[27] S.J. Kang, G.S. Mintz, T. Akasaka, D.W. Park, J.Y. Lee, W.J. Kim, S.W. Lee, Y.H. Kim, C. Whan Lee, S.W. Park, S.J. Park, Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation, Circulation 123 (2011) 2954–2963.

[28] T. Yonetsu, K. Kato, S.J. Kim, L. Xing, H. Jia, I. McNulty, H. Lee, S. Zhang, S. Uemura, Y. Jang, S.J. Kang, S.J. Park, S. Lee, B. Yu, T. Kakuta, I.K. Jang, Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry, Circ. Cardiovasc. Imaging 5 (2012) 660–666. American Heart Association, Inc..

[29] S.Y. Lee, S.H. Hur, S.G. Lee, S.W. Kim, D.H. Shin, J.S. Kim, B.K. Kim, Y.G. Ko, D. Choi, Y. Jang, M.K. Hong, Optical coherence tomographic observation of in-stent neoatherosclerosis in lesions with more than 50% neointimal area stenosis after second-generation drug-eluting stent implantation, Circ. Cardiovasc. Interv. 8 (2015) American Heart Association, Inc. (e001878–e001878).

[30] M. Kuroda, H. Otake, T. Shinke, T. Takaya, M. Nakagawa, T. Osue, Y. Taniguchi, M. Iwasaki, R. Nishio, H. Kinutani, A. Konishi, K.-I. Hirata, The impact of in-stent neoatherosclerosis on long-term clinical outcomes: an observational study from the Kobe University Hospital optical coherence tomography registry, EuroIntervention 12 (2016) e1366–e1374.

[31] C. Kim, B.K. Kim, S.Y. Lee, D.H. Shin, J.S. Kim, Y.G. Ko, D. Choi, Y. Jang, M.K. Hong, Incidence, clinical presentation, and predictors of early neoatherosclerosis after drug-eluting stent implantation, Am. Heart J. 170 (2015) 591–597.

[32] I. Andreou, P. Stone, In-stent atherosclerosis at a crossroads neoatherosclerosis or paleoatherosclerosis? Circulation 134 (2016) 1413–1415.