Neoatherosclerosis And Paleoatherosclerosis: Complications After Stenting

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Abstract

Neoatherosclerosis is a process of new in-stent atherosclerosis progression, it is now considered a common complication of percutaneous coronary intervention with drug-eluting stent. The development of neoatherosclerosis is a serious matter and can lead to the occurrence of late and very late stent thrombosis. Neoatherosclerosis poses a significant threat and increases the likelihood of experiencing acute coronary syndrome and angina. Paleoatherosclerosis is an advancement of pre-existing atherosclerosis, and it is also able to cause complications after stent implantation. In this review we concentrate on the atherosclerosis impact on stent restenosis and stent thrombosis, focusing on the differences between neoatherosclerosis and paleoatherosclerosis. They can lead to various complications including stent failure, although there is still much uncertainty surrounding these conditions. Numerous risk factors have been recognized that raise the likelihood of neoatherosclerosis progression, including the type of stent, kidney dysfunction, tobacco use, and low-density-lipoprotein (LDL) concentrations. These and other risk factors for neoatherosclerosis and paleoatherosclerosis development ought to be investigated in future studies in order to find causal connections and possible ways of alleviating these conditions.

Keywords: Neoatherosclerosis, Paleoatherosclerosis, Stent thrombosis, Percutaneous coronary intervention, Risk factors

Significance | Enhanced imaging techniques help in the comprehension of neoatherosclerosis and paleoatherosclerosis, which are crucial for preventing stent failure and improving treatment approaches.

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Introduction

It is widely acknowledged that neoatherosclerosis (NA) is an event frequently occurring after percutaneous coronary intervention with drug-eluting stent. The more intracoronary imaging, particularly optical coherence tomography, is used, the better the recognition and comprehension will get. Neoatherosclerosis can have serious consequences and may lead to late stent thrombosis. The pathological process entails formation of macrophages loaded with lipids inside the neointima (Lee et al., 2015). The emergence of NA increases the risk of acute coronary syndrome, symptoms of angina, and elevated toll-like receptors. Risk factors associated with a higher risk of NA include the type of implanted stent, smoking, chronic kidney disease, and LDL concentrations. Future researches can concentrate on these factors to mitigate the occurrence of this event. To gain a better understanding and treatment of this condition, it is essential to conduct prospective cohort studies using advanced cardiac imaging and possibly administer extended dual anti-platelet treatment (Upadhyay, 2015).

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The importance of stents in transdermal interventions cannot be overstated, however, their effectiveness may be negated by stent failure resulting from restenosis or thrombus formation, leading to significant morbidity and mortality (Gori, 2021). Even with advancements in device design and additional medical treatment, stent failure remains prevalent during extended monitoring. This implies that it may continue to be a long-term or even permanent concern. Multiple researches in the past several years have demonstrated that AS plays a substantial albeit previously not fully recognized role in stent failure (Clare et al., 2022).

Stenting as an advanced atherosclerosis treatment

Apart from medicinal treatments aimed at managing AS-related risk factors, there have been used various surgical methods including coronary artery bypass grafting, percutaneous coronary intervention, and carotid endarterectomy (CEA), with roughly 371,000, 480,000, and 86,000 procedures conducted, respectively, in the US in 2014 (Feldman et al., 2017). A number of randomized studies demonstrated that in individuals with advanced coronary artery disease (CAD) and diabetes, percutaneous coronary intervention was inferior to coronary artery bypass grafting. Percutaneous coronary intervention began as a basic balloon angioplasty to unblock obstructed vessels and improve the blood circulation. This technique frequently led to acute blockages due to arterial elastic recoil and formation of blood clots, which resulted in the narrowing of the vessels once again (Doggrell, 2013). In order to avoid these complications, the percutaneous coronary intervention was improved by adding bare-metal stent deployment and anti-platelet treatment to avert arterial elastic recoil and thrombus formation. Although, in-stent restenosis (ISR) continued to occur (Wang et al., 2018) (Figure 1).

To prevent restenosis, drug-eluting stents were introduced. This is the kind of stent that deploys sirolimus or other anti-proliferative drugs to the affected vascular region. First clinical studies of drug-eluting stents demonstrated positive results. In patients with drug-eluting stents neointimal overgrowth occurred less often and they were less likely to require revascularization (Puranik et al., 2013). However, after stent deployment the endothelial injury is unavoidable. Moreover, agents released by drug-eluting stents also suppress vascular reendothelialization since they are not cell-selective. Hereby, the initial version of drug-eluting stents raised significant safety concerns due to the emergence of NA and stent thrombosis. Stent thrombosis is a rare, but severe consequence of percutaneous coronary intervention which can lead to MI in 60-70% of cases and elevate the mortality risk by 20-25% (Habib and Finn, 2015).

Carotid endarterectomy (CEA) is also an effective method of revascularization designed to alleviate stenosis of the carotid artery. Multiple researches have demonstrated that the beneficial effects of stents and CEA are similar (Vasavada et al., 2023). To fight their related risks, the new variants of drug-eluting stents were developed, that are thinner and made of biocompatible polymers. Although, the new drug-eluting stents also release non-selective agents and raise the stent thrombosis risk in comparison to bare-metal stents. Hereby, even though the risk of hemorrhage is high, patients with drug-eluting stents require dual antiplatelet therapy (DAPT) (Koźlik et al., 2023). The experience with percutaneous coronary intervention suggests that therapeutic approaches for atherosclerosis (AS) have to take into account the priority of protecting the vascular endothelial cells (ECs) and target the pathogenic cells that facilitate the AS lesions development. This issue might be resolved using site-selective and cell-selective nano-therapy (Almas et al., 2022).

Neoatherosclerosis

As stent design was improving, a number of new complications were detected and supported by reliable subsequent information. For example, first drug-eluting stents decreased bare-metal stent related in-stent restenosis (ISR) rate considerably, but elevated the occurrence of in-stent thrombosis (IST). Interestingly, since neointimal overgrowth is the prevailing way of in-stent restenosis development, this condition happens earlier in individuals with bare-metal stents (Condello et al., 2023).

Drug-eluting stents (DESs) of second generation less often cause in-stent thrombosis then DESs of first generation. Although, another adverse effect of these stents has become known, it is referred as neoatherosclerosis. NA is a type of accelerated AS that progresses inside the damaged vascular segment and can result in late or vary late stent failure (Cui et al., 2016). NA is considered to be characterized by three different stages, including early infiltration by foam cells progression of in-stent AS lesions, and formation of necrotic core with a fibrous cap. In addition, in patients with drug-eluting stents of second generation, tissue properties differed in early (less than a year) and late (more than a year) in-stent restenosis (Nusca et al., 2022). The prevailing mechanism of early restenosis was overgrowth of neointima, and late restenosis was mostly mediated by NA. In particular, late ISR included higher occurrence of thin-cap fibroatheroma, neovascularization, neointima loaded with lipids, and infiltration by macrophages, than early in-stent restenosis. It can be concluded that slow healing of arteries caused by drug-eluting stents can predispose to NA. In patients with drug-eluting stents late stent failure rate is higher than in patients with bare-metal stents because of the stent insufficient expansion (Lee et al., 2018). Such condition is now considered a late or very late consequence of coronary intervention therapy. The autopsy study proved this idea and demonstrated that NA occurrence is notably higher in patients with drug-eluting stents than in patients with bare-metal

stents, with considerably shorter average duration of stenting in the first case (Kumar et al., 2022).

Furthermore, in drug-eluting stent implants NA progression was indicated as a "late catch-up" event because the growth of neointimal layer is inhibited in the first year after the drug-eluting stent placement, but then it progresses continuously along with quick accumulation of macrophages rich in lipids, hereby facilitating late stent failure. As expected, optical coherence tomography registry-based research of different versions of drug-eluting stents demonstrated that 3 most prevalent causes of very late drug-eluting stent failure are malapposition (34,5%), NA (27,6%), and uncovered struts (12,1%) (Park et al., 2012).

Risk factors associated with neoatheroslerosis

Although intracoronary imaging researches involving optical coherence tomography, intravascular ultrasound, and histopathologic tests allowed to gather some data on the compositional and morphological properties of NA, its pathophysiology and etiology are still unidentified. Several results of optical coherence tomography show that NA might develop irrespective of the stent type, instead influenced by focal triggers inside the artery which participate in the plaque formation (Gurgoglione et al., 2023).

The prevailing hypothesis about NA progression relies on the assumption that proliferation of neointima progresses inside the stent regardless of the plaque. Although, this view is based on a "snapshot" analysis of a neoatherosclerotic lesion and was disputed. The pathological mechanisms of AS and NA development are in fact similar (e.g., inflammation, endothelial dysfunction, lipid absorption) (Theofilis et al., 2021). Taniwaki and colleagues recently conducted research and demonstrated a substantial connection between in-stent NA and the native AS, evaluated as alterations of minimal lumen diameter (MLD) measured in respective coronary segments at baseline and five-year angiographic follow-up (Taniwaki et al., 2015). The research results showed a considerable decrease in minimal lumen diameter in target and non-target arteries in individuals with in-stent NA, which might indicate a connection between the two mechanisms. These results are even more important given the quite low occurrence of NA (16% in the research by Taniwaki) and the long-term follow-up that such patients require. It is noteworthy that higher presence of NA is not only related to individual AS risk factors, but also to non-traditional factors associated with design of the stent, anatomical properties of the lesion, local vascular hemodynamics, and variables related to the percutaneous coronary intervention (stent malapposition, inadequate expansion, fracture, etc.) NA was also found to be related to neovascularization and adjacent lipid plaques.

Development of NA also can be stimulated by changes in vascular hemodynamics. Endothelial shear stress (ESS) is a tangential stress caused by frictional force of circulating blood. ESS has an impact on development of AS in native and in stented vessels. A number of researches indicate that in human patients reduced endothelial shear stress might stimulate plaque development and formation of vulnerable plaques (Davies, 2009). Since pathological processes of NA and native AS share common characteristics, it can be concluded that hemodynamics and endothelial shear stress are essential in NA progression (Lupu et al., 2020). Papafaklis and colleagues performed a study that showed a negative correlation between endothelial shear stress and overgrowth of the neointima in patients with bare-metal stents and first versions drug-eluting stents (Papafaklis et al., 2010). An optical coherence tomography research demonstrated that NA is found more frequently in the inner curvature and at the outer bifurcation walls, that are usually subjected to low and oscillatory wall shear stress. Bourantas and colleagues conducted a virtual-histology intravascular ultrasound research that demonstrated that in individuals with bare-metal stents prevailing endothelial shear stress is inversely correlated to the contents of the neointimal necrotic nucleus, which is a sign of NA (Bourantas et al., 2012).

Both allergic and systemic inflammation are essential reactions to a foreign invader. These reactions are triggered by the placement of a stent and are related to stent thrombosis (ST), restenosis and severity of neointima lesion (Frodermann and Nahrendorf, 2018).

Pathophysiology of neoatherosclerosis and its clinical implications

Processes of NA and rapid formation of plaques after placement of drug-eluting stents are not yet fully understood. A number of studies were conducted on the atherogenic activity of perilipin and other lipid droplet (LD)-associated proteins, which contribute to the excessive deposition of lipids within cells and are associated with various disorders such as AS, adiposity, type 2 diabetes mellitus (Niccoli et al., 2018). Recent studies showed that adipophilin, also referred as perilipin 2 or ADRP, is involved in the in-stent restenosis progression because of NA in individuals with drug-eluting stents of second generation. Remarkably, concentrations of adipophilin were substantially lower in peripheral blood mononuclear cells (PBMCs) of individuals with native coronary artery disease in comparison to individuals with drug-eluting stents and in-stent NA (Alfonso et al., 2016; Borovac et al., 2019).

Fast formation of lipid-rich neointima and extensive foam cells infiltration at the region of the lesion are markers of NA, which suggests that elevated lipid deposition and storage in macrophages and monocytes that are recruited in higher amounts to the lesion are possibly the processes that contribute to the NA formation and

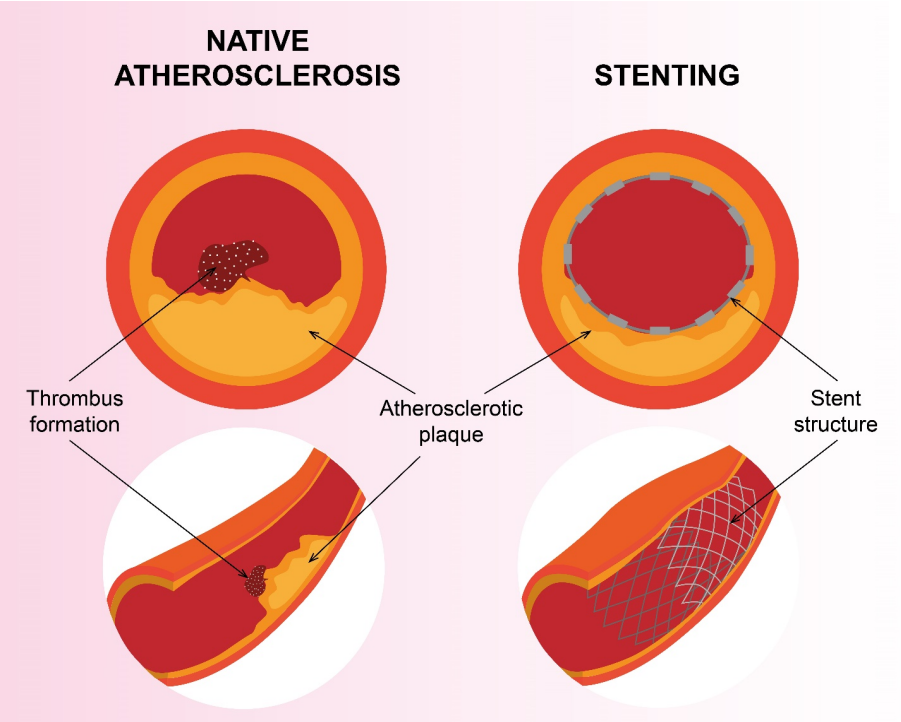

Figure 1. Stenting as an advanced approach of treating atherosclerosis

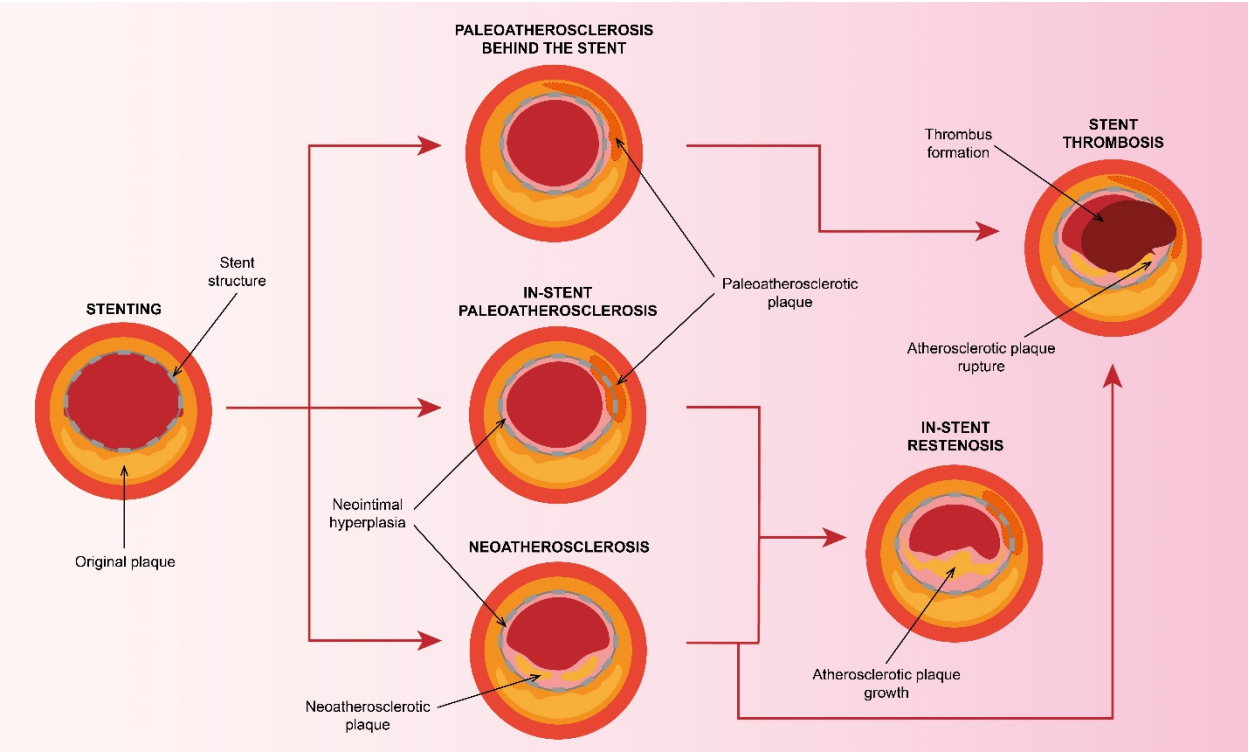

Figure 2. Neoatherosclerosis, paleoatherosclerosis and stent failure

development (Checkouri et al., 2021). In fact, adipophilin can mediate this effect, since the perilipin family of proteins has an important role in regulating cytoplasmic LD in foam calls and accumulation of cholesteryl esters CEs derived from altered lipoproteins. Recent studies indicated a considerable decrease in atheroma development and LD and CE components in cultures macrophages as a result of induced adipophilin deficiency and accompanying elevation of concentrations of cholesterol acceptors in plasma, including apoA1 and high-density-Lp cholesterol (Plakkal et al., 2016; Itabe et al., 2017).

Paleoatherosclerosis

Although paleo-AS role in complications after stent implantation was underestimated and unknown, currently available data indicate that its development and destabilization can greatly contribute to stent failure. Paleo-AS complications can be split into two groups: those that take place within the stent and cause stent thrombosis or in-stent restenosis and those that take place outside the struts and cause stent thrombosis (Gibbs et al., 1999).

Paleoatherosclerosis complications inside the stent

Since the beginning of cardiac surgery, the possible role of treated AS lesions in in-stent restenosis has been of interest. Currently, remnant AS plaques evaluated at the end of coronary interventions are considered strong independent predictors of in-stent restenosis. The plaque amount outside of the stent correlates with the amount of neointima hyperplasia, which is of importance in terms of bare metal stent (BMS) implantation (Redfors et al., 2018). These interesting discoveries suggest that the neointimal proliferation can mostly happen at the initial region of the AS lesion. That would mean that if a plaque is removed via additional atherectomy before the BMS placement, it could lower the risk of in-stent restenosis. However, no such connection has been found in various other researches which did not allow to finally determine the role of paleo-AS in irradiation stents (IRS) (Mitra and Agrawal, 2006)). On the contrary, some ultrasound studies of drug-eluting stents (DES) indicated that late in-stent proliferation of neointima is not connected to the remnant plaque amount. It has been suggested that initial AS plaque does not affect neointimal growth due to effect of the agent released by the DES. Although, is has been observed that a post-interventional AS plaque outside of the struts predicts neointimal overgrowth in two years after DES implantation (Nishino et al., 2019).

A number of researched have given additional information on the possible role of paleo-AS development in stent failure. It is noteworthy that AS progression inside the neointimal layer is typically observed in patients with signs of native AS, which might mean that pathological and etiological processes are similar. In an optical coherence tomography research, calcific neointimal tissue was found to be directly associated with the AS plaque underneath in 60% of all in-stent calcific AS lesions (Zhang et al., 2015). Another research showed a connection between the underlying necrotic core and in-stent AS plaque (consisting of cholesterol crystals, foam cells, and necrotic cell content). Furthermore, an intravascular ultrasound (IVUS) research showed that a reduction in the AS plaque site outside the struts was strongly correlated with the neointimal growth. This would mean a higher probability of a connection between the tissue within stent and the AS plaque underneath with possible tissue displacements through the struts (Montarello et al., 2020). The remodeling of narrowed arteries after stent implantation is likely to highly contribute to this condition. Moreover, an optical coherence tomography research indicated that severe tissue protrusion after stenting is an independent predictor of re-vascularization of the target lesion. Interestingly, in 96% of cases right after the stent placement, the struts were immersed in the destroyed AS plaque and the vessel segment was left with protruding parts of blood clots and plaques (Lee and Hur, 2019). This research showed that the location of the tissue protrusion within the stent after the surgery was consistent with that of the neointimal layer during the follow-up. Hereby, since plaque can bulge through the spaces between stent struts, AS lesions may remain above the stent struts after stent placement and develop in the neointima layer with time, which can be mistaken for NA during follow-up or at autopsy. On this basis, in pathology research, the unstable morphology of the underlying lesion has been considered a strong predictor for the in-stent AS progression. Hence, it may be suggested that after stent implantation the paleo-AS plaque can develop in the same way as native AS, growing slowly and gradually or rapidly with sudden alterations (Lee et al., 2017). This can cause different extent and rate of spread of the lesion, possibly through stent gaps, with subsequent narrowing of the lumen, which can stimulate in-stent restenosis. The plaque can rupture or burst, thus triggering stent thrombosis and acute coronary syndromes (ACS) or accelerated development of in-stent restenosis through repeated partial occlusions. Accordingly, recent optical coherence tomography studies reported that ruptures of the neointima can promote stent thrombosis (Abouelnour and Gori, 2022). Furthermore, plaque usually erodes in lesions loaded with smooth muscle cells (SMCs) and proteoglycans with desquamation of the endothelium, and this is one of the main causes of ACS. Human histopathological researches have in fact demonstrated that late and very late stent thrombosis may be due to the erosion of neointimal layer regardless of the presence of in-stent AS. Another serial optical coherence tomography evaluation demonstrated that stent thrombosis can be induced by eroded neointima, since all struts were embedded in atherosclerotic neointimal tissue without any evidence of the rupture of neointima (Luo et al., 2021). This can

shed light on the high frequency of in-stent restenosis manifesting as ACS, that is often related to irregularity of the surface of the vessel walls or thrombosis without signs of rupture. Thus, it can be hypothesized that in-stent restenosis with a focal pattern might indicate previous AS plaque complications, while diffuse-type restenosis may be a sign of excessive proliferation of the neointimal layer. Furthermore, recent optical coherence tomography researches discovered that about 33% of cases of very late stent thrombosis can be due to NA. Although, it is impossible to distinguish from paleo-AS, and hereby their proportion in the total number of cases is unknown (Zhang et al., 2022).

Paleoatherosclerosis complications behind the stent

There is still not enough clear evidence of paleo-AS development behind the stent struts. Although, the process of plaque formation within the stent that was mentioned above is likely to take place in the same way behind the struts along with arterial remodeling similar to native AS. According to thus, intracoronary imaging and autopsy researches indicated that late vessel healing with poorly covered stent struts and defective apposition of the stent are essential substrates for stent thrombosis (Andreou et al., 2016). Most of the cases of early and late stent restenosis and about 67% of cases of very late stent restenosis involved protrusion of the stent struts. Still, a causal connection has not yet been confirmed. Virtually, with low thrombogenicity of modern stents poor strut coverage and malapposition of stents happen quite frequently, although in most cases not leading to negative consequences (Condello et al., 2023). At the same time, a lot of patients with stent thrombosis do not show such results. On the contrary, in this case the paleo-AS plaque is susceptible to systemic risk factors, whereas local circulatory disorders may induce thrombogenic properties of blood and destabilize the plaque, hereby elevating the risk of thrombosis (Figure 2). Moreover, poor coverage of the stent struts can indicate delayed regeneration of the endothelium, which increases the likelihood of plaque disruption. Positive arterial remodeling is believed to be the predominant mechanism for evaginations, late malapposition and other findings related to stent thrombosis (Agostoni et al., 2010). This process probably can cause additional mechanical stress on the plaque leading to destruction of fibrous cap. There is a possibility that poorly covered or malapposed stent struts had been covered by the neointimal layer and appear to be epiphenomena at the moment of thrombosis because of disruption of neointima which exposed the struts. Hereby, poor coverage and malapposition of the struts are probably not the cause of stent thrombosis, but simply co-factors or paleo-AS plaque consequences (Mankerious et al., 2018). Accordingly, constituents of thrombus aspirates obtained from individuals with early vs. late stent thrombosis and in BMS vs. DES is mostly equal, which implies that pathological mechanisms are similar, calling into question the multifactorial etiology of stent thrombosis that is presently proposed. Moreover, similar to the case of native vascular atherothrombosis, leucocytes (eosinophils and neutrophils) and neutrophil extracellular traps (NETs) are the main constituents of thrombus aspirates (Tada et al., 2013). Notably, human histopathological trials showed that NETs and neutrophils are found in abundance in eroded AS plaques, but they are almost never found in uninjured plaques. These discoveries lead to conclusion that AS plaque complications may be the main mechanism for stent thrombosis irrespective of other related findings (Döring et al., 2020).

In the past years some hypotheses regarding this concept have been confirmed, such as in-stent AS promoting in-stent restenosis and disruption of neointima causing stent thrombosis (Figure 2). Whereas other ideas are still indeterminate (erosion of the neointimal layer), disputable (NA vs. paleo-AS role in stent failure), or theoretic (repeated disruption and healing of neointima causing in-stent restenosis, paleo-AS complications behind the struts) (Zhang et al., 2014).

Conclusion

A large percentage of cases of stent failure are associated with presence of atherosclerotic lesions of different etiology. Multiple studies demonstrate that atherosclerosis plays a major role in progression of in-stent thrombosis and in-stent restenosis, although in some cases the cause-and-effect relationship has not been fully understood. Several researches confirmed in-stent AS ability to promote in-stent restenosis, as well as the fact that neointimal disruption triggers stent thrombosis. However, a number of ideas remain conflicting, such as role of neointimal erosion in stent failure or repeated ruptures of neointima as a cause of in-stent restenosis. Discoveries associated with stent protrusions constitute a major part of all cases of stent thrombosis, although causality of these phenomena is also unclear. Poor coverage and malapposition of stent struts might contribute to the stent thrombosis or might just be co-factors. The utilization of intracoronary imaging, particularly optical coherence tomography, is expected to enhance awareness and comprehension. To gain a better understanding and effectively manage these disorders, it is crucial to conduct prospective cohort studies and potentially administer long-term dual anti-platelet treatment.

Author contribution

A.V.P. wrote, drafted; V.Y.G., V.N.S., A.N.O., R.V.G., D.F.B. wrote, reviewed, edited, VAK prepared the graph of the article. All authors have read and agreed to the published version of the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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