REVIEW ARTICLE

Stent thrombosis in patients with drug-eluting stents and bioresorbable vascular scaffolds: the feared complication

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KEY WORDS

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ABSTRACT

The percutaneous coronary intervention (PCI) has undergone rapid evolution over the last 40 years and has become one of the most widely performed medical procedures. The introduction of intracoronary stents has improved the safety and efficacy of PCI. However, with the advent of stenting, a new potentially fatal enemy has emerged: stent thrombosis. Ever since, adjunct pharmacological therapy, stent technique, and technology have been adjusted to reduce the risk of stent thrombosis. The aim of the present article is to provide an overview of the past, present, and future aspects of PCI in relation to stent thrombosis.

Introduction In the 1980s, the bare-metal coronary artery stent (BMS) was introduced, which has dramatically improved the safety and efficacy of percutaneous coronary intervention (PCI).[1,2] Although permanent scaffolding of the coronary vessel overcame the risk of abrupt vessel closure by dissection, acute closure of the stent by other mechanisms was recognized as an important complication. Acute closure of the metallic endoprosthesis, the so-called stent thrombosis (ST), is associated with high rates of morbidity and mortality.[3] Therefore, stent technology, implantation technique, and adjunct pharmacological therapy have been constantly adjusted to reduce the risk of ST. Now, 40 years after the first coronary balloon angioplasty, and despite all the advancement, percutaneous coronary therapy without restenosis or ST has not yet become a reality.

Definition of stent thrombosis In order to be able to compare the results of different clinical trials, the Academic Research Consortium defined ST according to various levels of certainty (TABLE 1).[4] The sensitivity and specificity of adjudicated ST event depends on the level of certainty.[5] In addition, the Academic Research Consortium made a classification of ST based on the time of occurrence (TABLE 1).[4]

Pathophysiology of stent thrombosis **Early stent thrombosis** The mechanisms of ST have been thoroughly investigated. Numerous patient-related, lesion-related, procedural and postprocedural factors are related to the occurrence of ST (TABLE 2). In the early phase, within 30 days after PCI, procedural factors are most likely responsible for ST, such as underexpansion, stent malapposition, residual dissection, tissue prolapse, and medial fracture.[6,7] Since the cause of early ST is mostly procedure related, the pathological findings are similar between various stents. Besides these procedural factors, stenting in acute coronary artery disease with high levels of thrombin is associated with high risk of ST.[8] In the early phase, platelets are exposed to nonendothelialized stent struts, thus optimal inhibition of platelet activation is the key factor of preventing early ST.[7] Clopidogrel resistance and discontinuation of dual antiplatelet therapy (DAPT) are essential risk factors of early ST.[9]

Late and very late stent thrombosis ST beyond 30 days after stent implantation is associated with delayed re-endothelialization characterized by persistence of fibrin and uncovered stent struts.[6,10] It takes at most 3 months for BMS to be covered by the endothelium, while endothelialization of early-generation drug-eluting stents (DESs) can take longer.[6] The delayed arterial healing in DES is likely responsible for the higher rates of late ST in early-generation DES.[10,11]

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TABLE 1 Definition of stent thrombosis according to the Academic Research Consortium

Level of certainty		
Definite ST	Angiographic or pathological confirmation of occlusion within the peri-stent region with clinical evidence of fresh thrombus	
Probable ST	Any unexpected death <30 days after PCI OR Any MI with documented acute ischemia in the territory of stented segment without angiographic confirmation of ST	
Possible ST	Any unexplained death >30 days after PCI	
Timing		
Early	Acute ST	<24 hours
	Subacute ST	24 hours to 30 days
Late ST		31 days to 1 year
Very late ST		>1 year

Abbreviations: MI, myocardial infarction; PCI, percutaneous coronary intervention; ST, stent thrombosis

TABLE 2 Predictors of stent thrombosis

Patient-related factors	Acute coronary syndromes, diabetes mellitus, smoking, renal failure, LVEF <30%, malignancy, prior brachytherapy, peripheral artery disease, nonadherence to antiplatelet therapy
Lesion-related factors	Lesion length, vessel diameter, complex lesions (bifurcation, chronic total occlusion), thrombus, saphenous vein grafts
Procedural factors	Stent undersizing/underexpansion, stent malapposition, stent deployment in necrotic core, dissection, stent length, overlapping stents
Postprocedural factors	TIMI flow grade <2 after PCI, premature cessation of antiplatelet therapy

Abbreviations: LVEF, left ventricular ejection fraction; TIMI, Thrombolysis in Myocardial Infarction; others, see **TABLE 1**

Other mechanisms in addition to delayed healing are important in the pathophysiology of very late ST. Hypersensitivity reaction due to polymer promotes macrophage reaction along with fibrin deposition and is associated with very late ST. Also extensive fibrin deposition leads to stent malapposition and is associated with ST.[6] Hypersensitivity reaction is rarely observed in patients with very late ST of BMS.

In addition, neoatherosclerosis of the stented segment is observed in patients with very late ST. Neoatherosclerosis following stent implantation is likely multifactorial. Newly formed atherosclerotic plaques contain peri-strut foamy macrophage clusters or fibroatheromas with necrotic core formations. The incidence of neoatherosclerosis is greater in lesions associated with DES than those with BMS.[6]

Past **Bare-metal stents** In the early days of intracoronary stenting, with low-pressure inflation and single antiplatelet therapy, the use of BMSs was associated with approximately 20% of ST cases.[1] The use of aspirin in combination with warfarin reduced the rate of ST to 3.5% but led to more hemorrhagic complications.[2,12] In 1995, Colombo et al[13] introduced DAPT with low-dose aspirin and thienopyridine, and optimized stent implantation using high-pressure balloon inflation under intravascular ultrasound imaging. This combination led to an ST rate of 1.6% at 6-month follow-up and favored the dissemination of BMS use. However, stent implantation causes arterial injury resulting in excessive neointimal proliferation, which may result in restenosis.[14] Restenosis, which leads to a need for revascularization, occurred in up to 30% of the patients treated with BMS and is the key limitation of BMS.

Early-generation drug-eluting stents To address the main limitation of BMS, metallic stents are coated with cytostatic drugs. The early-generation DES consists of 3 components: a stainless-steel stent platform with strut thickness of 130 to 150 μm, an antiproliferative agent, and a durable polymer coating. The polymer coating allows an effective and controlled antiproliferative drug release. The first trials showed that, indeed, DES markedly reduced restenosis and the need for revascularization at 6-month follow-up compared with BMS.[15,16] The Initial Double-Blind Drug-Eluting Stent vs Bare-Metal Stent Study (RAVEL) showed a reduction of 100% in restenosis (luminal narrowing of 50% or more) at 6 months with sirolimus-eluting stent as compared with BMS (0% vs 26.6%, respectively).[15] However, the initial enthusiasm was slowly tempered by growing concerns over an increased risk of late and very late ST. Later, registry data published by Daemen et al[17] demonstrated a steady risk for ST of 0.6% per year after DES implantation. Thus, the first-generation DES overcame the shortcomings of BMS by reducing the restenosis rate but introduced another problem, namely, late and very late ST. Pathological studies elucidated the underlying pathophysiology of these adverse events. The durable polymer, the thickness of the stent struts, the dose of the antiproliferative drug and its release kinetics were important factors contributing to the occurrence of ST after DES implantation,[6] in particular the durable polymer. The durable polymer could result in chronic arterial wall inflammation and impaired endothelial healing of the stented segment, which increases the risk of ST.[6]

Present **New-generation drug-eluting stents** New-generation DESs have improved antiproliferative drug release kinetics, thinner stent struts, and more biocompatible or biodegradable polymer coatings. The new-generation DESs are based on novel metallic alloys, such as cobalt-chromium and platinum-chromium, allowing thinner stent struts (50–100 μm) while maintaining an adequate radial strength. Thinner stent struts (<100 μm) improve hemodynamic flow with a relatively lower shear stress over the struts, favoring vessel healing of the stented segment.[18] In addition, thinner stent struts have a lower degree of thrombogenicity in comparison with thicker

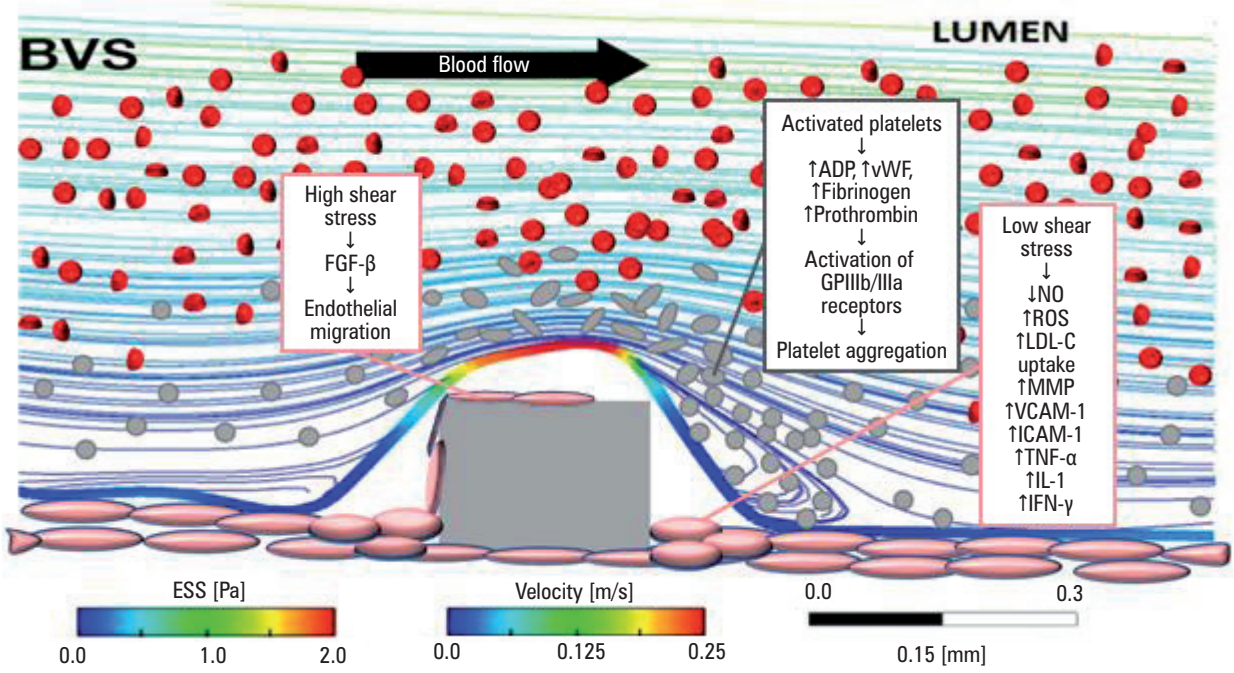

FIGURE 1 Shear stress. The implanted stent strut and the changes in flow in the vicinity of the strut are shown. The red blood cells (RBCs) (red filled circular structures) tend to accumulate towards the center of the lumen; the platelets (grey filled circles) are pushed to the vessel wall by the RBCs. When they move in a faster flow zone passing over the strut top surfaces, the platelets are elongated and activated. After crossing the faster flow zone, the platelets enter a reversing flow zone. Since the flow velocity decreases in these reversing flow zones, platelets resume their original discoid shapes and release several growth factors. The ESS bar codes the shear stress levels over the intimal layer and the strut. The velocity bar codes the velocity of the flow streamlines in the vessel lumen.

Abbreviations: ADP, adenosine diphosphate; BVS, bioresorbable vascular scaffolds; FGF-β, fibroblast growth factor β; GP IIb/IIIa, glycoprotein IIb/IIIa; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon γ; IL-1, interleukin 1; LDL-C, low-density lipoprotein cholesterol; MMP, matrix metalloproteinase; NO, nitric oxide; ROS, reactive oxygen species; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; vWF, von Willebrand factor

struts. Moreover, stents with thinner struts cause less vessel injury at implantation. Penetration of necrotic tissue is associated with the occurrence of ST.[19] The effect of stent strut in the vessel wall on blood flow and the biochemical reactions are depicted in FIGURE 1.

In addition, new-generation DESs have been developed with improved biocompatibility of the polymer coating. Also, some stents have been developed with a biodegradable polymer. Once the antiproliferative drugs are completely released, the polymer coating has no function. Therefore, the biodegradable polymers are fully resorbed by hydrolysis after the completion of drug release. Several new-generation DESs have been designed and approved for European use.

Numerous studies have shown a favorable safety and efficacy of new-generation DES compared with early-generation DES.[20,21] Some meta-analyses have also shown that new-generation DESs have a decreased risk of ST compared with BMSs.[21] Especially the XIENCE durable–polymer-based everolimus-eluting stent showed improved safety compared with other stents.[21] However, the risk of ST remains and is very unpredictable, so the search for the optimal stent design continues.

Bioresorbable vascular scaffolds To overcome the shortcomings of a permanent metallic stent, such as abnormal vasomotion and neointimal proliferation, which contribute to the risk of very late ST,[6,10,22] bioresorbable vascular scaffolds (BVSs) have been developed. BVSs were designed to provide transient mechanical support with drug delivery similar to that of DES during the required period, followed by complete bioresorption over several years. In the absence of a rigid metallic cage, there would be no potential triggers for thrombosis, such as uncovered stent struts, malapposition, and drug or durable polymer. Thereby, complete bioresorption can theoretically facilitate the restoration of the vasomotor tone, adaptive shear stress, late luminal enlargement, and late expansive remodeling.[23-25] All this contributes to a better vascular healing and reduces the need for revascularization.

Early studies of the Absorb BVS (Abbott Vascular, California, United States) noted noninferiority of safety and efficacy at 1-year follow-up compared with metallic DES.[26] This led to approval by the Food and Drug Administration and clinical adoption of the device. However, concerns regarding scaffold thrombosis emerged from the results of the Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial (AIDA). Absorb had more device-related ST with a mean follow-up of 707 days compared with metallic DES (3.5% vs 0.9%; P <0.001).[27] Meta-analyses of the Absorb

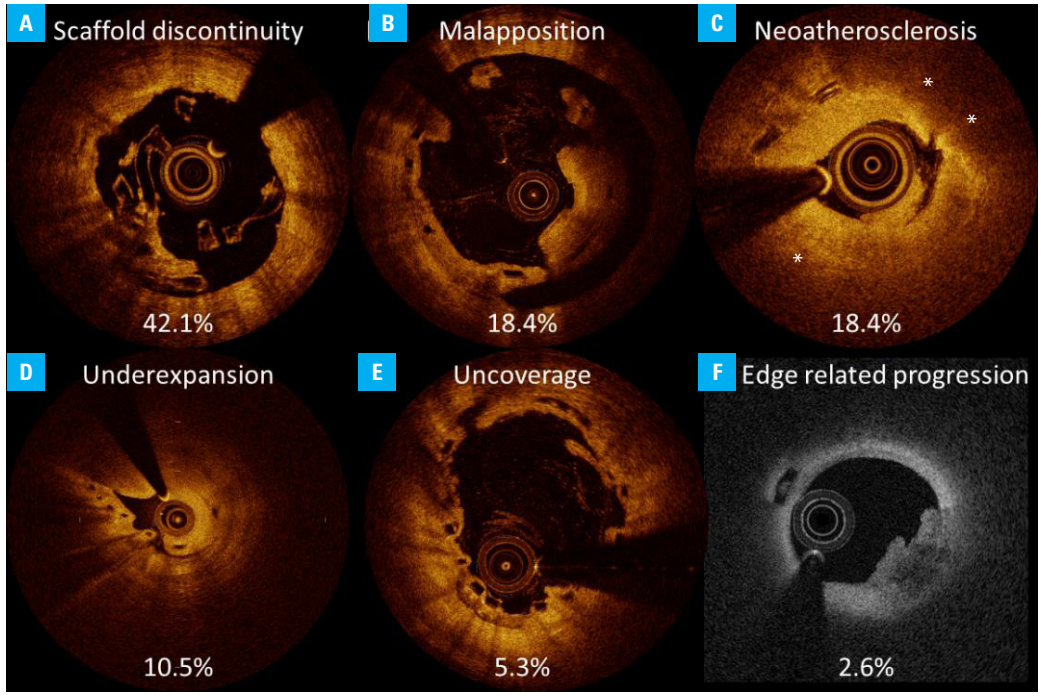

FIGURE 2
Representative images and frequencies (%) of the mechanisms underlying very late scaffold thrombosis, including scaffold discontinuity (**A**); malapposition (**B**), neoatherosclerosis (**C**), underexpansion (**D**), uncoverage (**E**), edge--related progression (**F**). Light attenuation due to lipid accumulation within the neointima of the scaffold (asterisks) (reproduced with permission from Yamaji et al)[34]

studies confirmed these results.[28,29] Ali et al[28] performed a patient-level meta-analysis of the Absorb randomized trials and found higher rates of device thrombosis during 3-year follow-up with BVS (2.4% vs 0.6%; P = 0.001). After these observations, Abbott has ended commercial sales of the Absorb BVS.

The mechanisms of early scaffold thrombosis seems to be similar to that of early ST after BMS or DES implantation, including procedural factors such as device underexpansion, malapposition, and undersizing.[30-32]

Delayed healing with uncovered struts of the stented segment was the primary cause of late ST in first-generation DESs with thick struts (~140 μm).[33] Because the polymeric structure of the BVS is not as strong as metal, Absorb BVS have thick struts (157 μm) to improve its radial strength. In addition to these thick struts, other mechanisms seemed to contribute to late and very late scaffold thrombosis. Malapposition and scaffold discontinuity are mostly associated with late or very late scaffold thrombosis.[34,35] Scaffold discontinuity suggests an unfavorable scaffold bioresorption progress. Before the struts disappear, they lose their structural integrity which might lead to intraluminal dismantling of the scaffold.[36] The discontinuous struts can penetrate into the lumen and cause disruption of the laminarity of flow with subsequent activation of the coagulation cascade, which may end up in thrombus formation and vessel occlusion.[37-39] Even after optimal implantation of BVS, the thicker quadratic struts may induce disruption in a local microhemodynamic environment and result in lower shear stress zones in the vicinity of the struts engendering a well-established area for thrombus formations, which entails thinner and streamlined design of the struts.[40] The different underlying mechanisms and frequency of very late scaffold thrombosis are illustrated in FIGURE 2.

Intracoronary imaging Emergency PCI is the preferred treatment for ST. Coronary angiography provides a 2-dimensional representation of the 3-dimensional arteries. It shows luminal dimensions and characteristics without providing any information on the arterial wall. This modality is also suboptimal in identifying stent underexpansion, malapposition, residual dissection, thrombus or plaque protrusion, all known triggers for ST. Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) overcome these limitations and can visualize the underlying mechanisms causing ST.[41,42] Intravascular imaging with IVUS or OCT can be safely performed after stabilization of the clinical status of the patient. The underlying cause of ST influences the treatment of the affected segment. When stent malapposition is the cause of ST, high-pressure balloon angioplasty suffices, but when stent edge dissection is the underlying problem, implementation of a new stent is advised.

In addition, intravascular imaging after PCI will optimize stent implantation by immediately detecting stent underexpansion, malapposition, or edge-related dissections and thereby, in theory, will reduce the change of ST. Large observational cohort studies, randomized trials, and meta--analyses have shown that IVUS-guided stent implantation reduces the rate of major adverse cardiac events, including ST, compared with angiography guidance alone.[43,44] Despite these findings and guideline recommendations,[45] IVUS-guided PCI is rarely used. Low resolution (150–200 μm), slow pullback, and absence of accurately powered randomized trials are often mentioned as the grounds for the low levels of adoption of IVUS in standard care.

OCT is a newer intravascular imaging method and provides high-resolution images (10–20 μm).[46,47] OCT is more accurate than IVUS in detecting morphological details during PCI, including malapposition, plaque prolapse, residual thrombus, and residual dissections after stent implantation. During follow-up after PCI, OCT is also superior to IVUS for the assessment of neointimal thickness, strut apposition, and strut coverage.[48,49] Nonetheless, fewer clinical studies of OCT-guided stenting have been conducted. Prati et al[50] showed that angiography plus OCT-guidance resulted in lower rates of cardiac deaths, myocardial infarction (MI), and the composite endpoint of cardiac death, MI, or repeat revascularization at 1-year follow-up compared with coronary angiography guidance. The addition of the OCT guidance was independently associated with a lower risk of cardiac death or MI (odds ratio, 0.49; 95% confidence interval 0.25–0.96; $P = 0.037$). However, previous studies showed that OCT may lead to the choice of a smaller stent diameter and is associated with smaller lumen compared with IVUS or coronary angiography.[51] Moreover, OCT required an additional intracoronary injection of contrast media to enable visualization.[52] The volume of contrast media should be taken into account since contrast nephropathy is one of the major causes of in-hospital and long-term mortality and morbidity after PCI.[53] Therefore, OCT is not yet a standard procedure during PCI.

A recent randomized clinical trial showed that a novel OCT-based stent sizing strategy resulted in a similar minimum lumen area as IVUS-guided stent implantation.[52] Whether this new strategy with OCT will result in better clinical outcomes is unknown. This issue will be addressed in the upcoming ILUMIEN IV randomized trial.

Antiplatelet therapy Antiplatelet therapy has become essential after PCI for primary prevention of ST and secondary prevention of ischemic thrombotic events. In 1977, when the first in-man percutaneous transluminal coronary angioplasty was performed, aspirin was given before the procedure, followed by warfarin administered after the procedure and continued for 6 to 9 months.[54] The use of aspirin in combination with warfarin improved clinical outcomes with a reduction of the ST rate from 20% to 3.5%, but this combination led also to excessive bleeding complications.[2]

Colombo et al[13] and Schömig et al[55] reported that treatment with DAPT (aspirin plus ticlopidine) up to 1 month after PCI reduced the incidence of both ST and hemorrhagic complications compared with anticoagulant therapy (warfarin plus aspirin).[56] Clopidogrel was found to be a safer alternative to ticlopidine.[57] DAPT with aspirin plus clopidogrel became the standard therapy following PCI. When DESs were investigated for the first time, duration of DAPT was prolonged to 3 months in the SIRIUS study (Sirolimus-Coated BX VELOCITY Balloon-Expandable Stent in Treatment of De Novo Coronary Artery Lesions)[58] and up to 6 months in TAXUS-IV trial (Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent).[59] The duration of DAPT was prolonged to reduce the rates of restenosis and associated clinical events, but the optimal duration has not been investigated in randomized clinical trials. Once the increased risk of late ST after early-generation DES implantation was noticed, the duration of DAPT was prolonged even further to 1 year after PCI. This led to the guidelines' recommendation of DAPT for at least 6 months following DES implantation in patients with stable coronary artery disease and 12 months in those with acute coronary syndromes.[60] These recommendations still apply today. However, they are based on weak evidence, and the optimal duration of DAPT remains undetermined.

To provide evidence supporting the consensus guideline recommendations, extensive research investigating the optimal duration of DAPT have been done. These studies have been focused on 2 main strategies: abbreviated and extended DAPT regimens. The duration of prolonged DAPT ranged from 18 months to 4 years, which was compared with a 12-month DAPT regimen. Similar rates of adverse events between the regimens were observed in all trials. The small benefit in terms of very late ST prevention does not seem to be justified against the risk of bleeding related to DAPT prolongation.[61-64]

Around 6% of the patients with acute coronary syndrome do not respond to clopidogrel therapy.[65] Buanamici et al[9] showed this nonresponsiveness to be independently associated with a higher risk of ST. The advent of novel potent $P2Y_{12}$ receptor inhibitors and the refinements in DES technology have resulted in a shift from the belief that DAPT duration should be extended to abbreviated DAPT. In studies on shorted DAPT, 12-month DAPT was, in general, compared with either 3- or 6-month DAPT. All those trials demonstrated noninferiority but no superiority of the abbreviated DAPT regimen.[66-69] Of note, the results should be carefully interpreted due to the use of different definitions of major adverse cardiac events and major bleeding. In addition, the trials tested for noninferiority of net adverse cardiac events between DAPT regimens. In this approach, minor bleeding and ST obtain the same value.

In addition, it is thought that ticagrelor may also provide inhibition of the cyclooxygenase-1 pathway.[70] If this is correct, ticagrelor monotherapy will maintain efficacy compared with the combined use of aspirin and ticagrelor while improving safety. Two worldwide randomized trials of ticagrelor monotherapy are ongoing, and the results will be presented soon.[71,72]

Future perspectives Overall, the impressive development of PCI technology—particularly coronary stents—has changed the standard treatment of ischemic heart disease. Nowadays,

new-generation DESs are the standard of care for patients undergoing PCI. However, although uncommon, ST still occurs and is feared due to the strong association with mortality.[3] Thereby, ST is still unpredictable. The permanent metallic cage represents a potential trigger for ST in the years after implantation. This is particularly relevant in otherwise healthy patients with a long life expectancy. Whether liberation of the metallic stent and restoration of the vascular physiology may translate into clinically meaningful benefits without ST will be evaluated in future studies after advances in the scaffold technologies have been made.

In addition, an improvement of stenting in the subgroups of clinically or anatomically complex patients is needed. Patients with diabetes are characterized by more advanced and complex coronary artery disease. Despite the improvement in metallic stent technology, diabetes remains an independent predictor of ST.[73] Clinical outcomes of patients with diabetes might be improved by increased antirestenotic potency of the metallic stent. Sardella et al[74] showed promising results of a dedicated DES with antiproliferative agent amphilimus—a formulation of sirolimus and organic acids—used in diabetic patients. However, these results require further confirmation in large-scale randomized clinical trials.

The treatment strategy for lesions in the small vessels, in-stent restenosis, and bifurcation lesions also needs improvement. Recently, sirolimus-coated balloons have been developed. Preclinical trials showed encouraging results for this method.[75] There are several ongoing trials investigating the use of sirolimus-coated balloons for complex lesions instead of DESs. A registry of 277 patients with complex lesions demonstrated that sirolimus-coated balloon angioplasty is effective in complex lesions (EuroPCR presentation, 2016).[76] If the other trials show similar results, drug-coated balloons will get a more resilient role in PCI.

The optimal duration of DAPT is still a matter of debate. Not only should the optimal PCI strategy be personalized by considering the anatomical aspects and comorbidities in individual patients, but also the duration of DAPT should be tailored based on the assessment of the risk–benefit ratio. Several risk scores have been created and validated,[77,78] but no prospective clinical trials testing these scores have been performed yet. In the future, the choice and duration of antiplatelet therapy may be guided more by the general patient's risk profile using the risk scores. In case of acute coronary syndromes, it is also possible that DAPT will change into dual pathway regimen combining a novel oral anticoagulant with a $P2Y_{12}$ receptor inhibitor, blocking fibrin formation and inhibiting platelet activation and aggregation.[79]

To remember DAPT is mandatory after stent implantation for primary prevention of ST and secondary prevention of ischemic thrombotic events. A premature cessation of DAPT is a strong predictor of ST.[73] It takes time before the stent is re-endothelialized, and until then, the discountination of DAPT can be fatal and lead to ST. Because ST is associated with a high mortality rate of around 20%,[3] cessation of DAPT should always be decided in consultation with an interventional cardiologist. The duration of DAPT depends on the indication for PCI, type of stent, complications that may have occurred during PCI, and contraindications.[80,81] The interventional cardiologist has the expertise to assess the risks of DAPT cessation.

Moreover, the choice of treatment for significant coronary artery disease will be also influenced by other needed interventions or treatments. If a patient needs chemotherapy or surgery—treatments with high risk of bleeding—the choice of stent will be different from that in a patient without these upcoming treatments.[82] Collaboration between different specialists is important for patients with multimorbidity.

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