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Abstract

Stent thrombosis is a rare complication following stent implantation; if it occurs, however, it is associated with a high morbidity and mortality. Despite reduced rates of restenosis, drug-eluting stents (DES) have not reduced the incidence of stent thrombosis as compared with bare-metal stents (BMS). Patient-, lesion-, and procedure-related factors as well as thrombogenicity of the stent itself are involved in the pathogenesis of stent thrombosis. Furthermore, early cessation of dual antiplatelet therapy correlates with an increased risk of stent thrombosis. This review focuses on clinical evidence and pathophysiological mechanisms of stent thrombosis with DES, particularly highlighting prothrombotic effects of the stent itself.
Drug-Eluting Stent Thrombosis

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ABSTRACT

Stent thrombosis is a rare complication following stent implantation; if it occurs, however, it is associated with a high morbidity and mortality. Despite reduced rates of restenosis, drug-eluting stents (DES) have not reduced the incidence of stent thrombosis as compared to bare-metal stents (BMS). Patient-, lesion-, and procedure-related factors as well as thrombogenicity of the stent itself are involved in the pathogenesis of stent thrombosis. Furthermore, early cessation of dual antiplatelet therapy correlates with an increased risk of stent thrombosis. This review focuses on clinical evidence and pathophysiological mechanisms of stent thrombosis with DES, particularly highlighting prothrombotic effects of the stent itself.

KEY WORDS

Acute coronary syndrome, drug-eluting stent, stent thrombosis, reendothelialization, tissue factor
Percutaneous coronary intervention (PCI) is a routine interventional procedure for treating acute coronary syndromes. The use of bare-metal stents (BMS) reduced restenosis rates as compared to angioplasty alone from \(\approx 40\%\) to \(\approx 20\%\) [Babapulle et al. 2004; Grines et al. 1999]. Drug-eluting stents (DES), coated with antiproliferative agents such as rapamycin or paclitaxel, further decreased rates of restenosis to less than 10\% and improved the outcome after coronary artery stenting [Babapulle et al. 2004; Windecker et al. 2005].

However, major concerns emerged about the safety of DES, particularly regarding the incidence of stent thrombosis [Camenzind et al. 2007; Daemen et al. 2007; Lagerqvist et al. 2007; Mauri et al. 2007; Pfisterer et al. 2006]. Despite reduced rates of restenosis, the incidence of stent thrombosis may be higher with DES as compared to BMS. In particular, late stent thrombosis can occur months or even years after stent deployment in patients treated with DES [McFadden et al. 2004; Daemen et al. 2007; Holmes et al. 2007; Lüscher et al. 2007].

The incidence of stent thrombosis with BMS was reported to be \(\approx 1\%\) [Babapulle et al. 2004; Cutlip et al. 2001; Holmes et al. 2007]. BMS thrombosis mostly occurred within the first 30 days after implantation; however, late thrombotic events have been documented as well [Doyle et al. 2007; Stone et al. 2007]. During the first months after stent deployment, the rates of stent thrombosis did not differ between patients treated with BMS and those treated with DES [Iakovou et al. 2005; Moreno et al. 2005; Ong et al. 2005; Windecker et al. 2005]; the incidence was 1.0\% to 1.5\% within the first 30 days, and 0.5\% between 1 and 9 months. However, in the BASKET (Basel Stent Kosten Effektivitäts Trial)-LATE trial, late stent thrombosis was observed twice as frequently after DES deployment as compared to BMS, particularly
following cessation of antiplatelet therapy. In this trial, the incidence of thrombosis was 2.6% in DES versus 1.3% in BMS between 7 and 18 months after stent deployment [Pfisterer et al. 2006].

Recent data indicate that stent thromboses with DES do indeed continue to occur steadily. Rates of 0.3-1.1% per year for at least up to 3 years after stent implantation have been observed [Daemen et al. 2007; de la Torre-Hernández et al. 2008; Flores-Ríos et al. 2008]. However, the true incidence of late thrombosis is not clear to date.

Stent thrombosis is a relatively rare complication after stent implantation; however, given the large number of coronary interventions and the serious nature of this complication, it remains a major concern [Holmes et al. 2007; Iakovou et al. 2005]. Cardiac death and myocardial infarction have been observed in 4.9% of patients after DES deployment as compared to 1.3% after BMS deployment 7 to 18 months after stenting, possibly related to late stent thrombosis [Pfisterer et al. 2006]. Consistently, in a large clinical registry, an increased risk of cardiac death and myocardial infarction was observed 6 months to 3 years after DES implantation when compared to BMS [Lagerqvist et al. 2007]. However, after long-term follow-up, the overall incidence of cardiac death and myocardial infarction was reported to be similar in both stent groups [Lagerqvist et al. 2007; Pfisterer et al. 2006; Spaulding et al. 2007; Stettler et al. 2007]. These findings have been related to increased rates of death and myocardial infarction during the initial 30 days as well as higher rates of restenosis related cardiac events after BMS deployment [Doyle et al. 2007; Lagerqvist et al. 2007; Pfisterer et al. 2006; Spaulding et al. 2007].

Stent implantation for off-label indications such as restenotic lesions, bypass graft lesions, left main coronary artery disease, as well as ostial, bifurcated, and totally occluded lesions is common practice. Off-label use of both, DES and BMS,
has been associated with higher rates of ischemic complications as compared with standard indications [Beohar et al. 2007; Win et al. 2007; Marroquin et al. 2008]. However, among patients with off-label indications, the incidence of death and myocardial infarction was reported to be similar in both stent groups 1 year after stent deployment [Marroquin et al. 2008]. These findings suggest that the poorer outcome observed after stenting for off-label indications are related to patient and lesion characteristics but not to the stent itself. As observed with standard indications, DES implantation may be associated with lower rates of repeated revascularization as compared with BMS [Marroquin et al. 2008]. Hence, large long-term randomized clinical trials including different clinical subsets of patients undergoing DES deployment for standard indications as well as for off-label use are needed to ascertain the safety of DES and fully assess the risk of late stent thrombosis.
Several factors are involved in the pathogenesis of stent thrombosis [Figure 1]. Patient-related factors such as diabetes mellitus, renal failure, advanced age, low ejection fraction, and stenting in acute coronary syndromes are associated with an increased risk of stent thrombosis [Iakovou et al. 2005]. Furthermore, advanced age seems to be a risk factor for subacute stent thrombosis, whereas younger age has been associated with late stent thrombosis [de la Torre-Hernández et al. 2008]. Lesion-related factors such as bifurcation lesions, lesion length, and restenosis lesions also promote the occurrence of thrombotic events; moreover, procedure-related factors such as stent malapposition, subexpansion, overlapping stent placement, and coronary artery dissection predispose to stent thrombosis [Farb et al. 2003; Iakovou et al. 2005; Joner et al. 2006; Finn et al. 2007]. Indeed, incomplete stent apposition has been observed more frequently after DES implantation as compared to BMS, which may further contribute to late thrombotic events [Hong et al. 2006; Qian et al. 2008].

**Discontinuation of Antiplatelet Therapy**

Dual antiplatelet therapy with clopidogrel and acetylsalicylic acid plays a key role in reducing the incidence of thrombotic events, associated death, and myocardial infarction after stent implantation [Grines et al. 2007; Eisenstein et al. 2007]. Particularly during the first 6 to 12 months after stent deployment, discontinuation of dual antiplatelet therapy has been shown to increase the risk of DES thrombosis [McFadden et al. 2004; Windecker et al. 2007]. However, cessation of clopidogrel has recently been associated with higher rates of death and myocardial infarction 2 years after DES deployment [Eisenstein et al. 2007]. Furthermore, stent
thromboses have been observed after interruption of longterm antiplatelet monotherapy [Flores-Ríos et al. 2008; McFadden et al. 2004]. In addition, nonresponsiveness to antiplatelet therapy may further promote thrombus formation after stent implantation [Grubel et al. 2007].

At present, a course of 12 months of dual antiplatelet therapy with clopidogrel and acetylsalicylic acid may be considered. Dual antiplatelet therapy with prasugrel for 6 to 15 months was recently shown to reduce the incidence of stent thrombosis, cardiovascular death, myocardial infarction, and stroke as compared to clopidogrel [Wiviott et al. 2008]. Hence, optimal antiplatelet therapy, its duration, and the use of BMS if contraindications prevent dual antiplatelet therapy remain to be determined to reduce the incidence of stent thrombosis.

**Inflammatory Reaction to the Stent**

Stent length and strut thickness correlate with an increased risk of stent thrombosis. As shown in autopsy studies, inflammatory reactions predominantly mediated by CD45-positive leucocytes and eosinophils take place after stent implantation. Eosinophilic infiltrates around struts reflect a hypersensitivity reaction to the stent, most likely the polymer [Nebeker et al. 2006; Virmani et al. 2004]; however, reactions to the metal struts or the loaded drugs may also contribute. Indeed, inflammatory reactions are more pronounced after DES implantation as compared with BMS [Farb et al. 2003; Joner et al. 2006; Finn et al. 2007]. In the rabbit iliac artery stenting model, stronger inflammatory reactions, more fibrin deposition, and an incomplete reendothelialization are observed after DES implantation as compared to BMS [Finn et al. 2005]. Hence, inflammatory response and hypersensitivity reaction
to the stent delay vascular healing and may thereby favor thrombotic events, particularly after DES deployment.

**Impaired Reendothelialization**

Stent deployment causes endothelial denudation and exposes thrombogenic material to the circulating blood. Hence, complete reendothelialization of the stented segment is crucial for vessel healing. Reendothelialization is completed 2 weeks after BMS implantation in the porcine coronary artery and 3 to 4 weeks after BMS deployment in the rabbit iliac artery [Finn et al. 2007]. In contrast, only 40% to 60% of the stent surface is reendothelialized after DES deployment at the same time points [Finn et al. 2005 and 2007]. Angioscopic findings in humans revealed that complete reendothelialization was achieved 3 to 6 months after BMS deployment, whereas the majority of rapamycin-eluting stents exhibited incomplete neointimal coverage [Kotani et al. 2006]. These findings were complemented by human autopsy studies showing impaired arterial healing characterized by incomplete reendothelialization and persistent fibrin deposition after DES implantation as compared to BMS [Joner et al. 2006; Finn et al. 2007].

The macrocyclic lactone rapamycin and the microtubule-stabilizing agent paclitaxel are both used on first-generation DES and reduce restenosis by inhibiting vascular smooth muscle cell proliferation as well as migration [Parry et al. 2005; Sollott et al. 1995]. Everolimus and zotarolimus, used on second-generation DES, exert a similar inhibitory effect on vascular smooth muscle cell activation [Farb et al. 2002; Garcia-Touchard et al. 2006].

Since these drugs do not act in a cell-type specific manner, it is conceivable that agents eluted from DES do not only affect vascular smooth muscle
cells, but also alter the biology of endothelial cells. In addition to their effect on vascular smooth muscle cells, rapamycin, paclitaxel, and zotarolimus do indeed inhibit proliferation and migration of endothelial cells [Matter et al. 2006; Parry et al. 2005; Steffel et al. 2005; Garcia-Touchard et al. 2006]. Thus, agents eluted from DES impair endothelial regeneration by inhibiting proliferation and migration of these cells, and the impaired endothelial coverage after stent deployment leaves the thrombogenic stent struts in contact with the circulating blood favoring the development of thrombosis.

Endothelial progenitor cells are the circulating precursors of mature endothelial cells and contribute to neovascularization and healing at sites of endothelial damage. Hence, a crucial role has been ascribed to these cells in the process of reendothelialization [Blindt et al. 2006; Griese et al. 2003]. Interestingly, rapamycin negatively affects proliferation, migration, and differentiation of human endothelial progenitor cells [Butzal et al. 2004; Chen et al. 2006]. Thus, drugs eluted from DES may further delay vascular healing by impairing proper function of endothelial progenitor cells.

**Enhanced Tissue Factor Expression**

Given the important role of tissue factor (TF) as the principal trigger of coagulation, TF may also be involved in the pathogenesis of stent thrombosis [Steffel et al. 2006; Steffel et al. 2007]. Both rapamycin and paclitaxel do indeed enhance TF expression and activity under inflammatory conditions; rapamycin enhances thrombin- and TNF-α-induced TF expression via inhibition of the mammalian target of rapamycin (mTOR) [Steffel et al 2005], whereas paclitaxel increases TF expression via c-Jun terminal NH₂ kinase (JNK) activation [Figure 2] [Stähli et al. 2006].
Interestingly, both rapamycin and paclitaxel also increase plasminogen activator inhibitor (PAI)-1 expression in human coronary artery endothelial cells [Muldowney et al. 2007]. Because of their lipophilic properties, both rapamycin and paclitaxel accumulate in the vessel wall, reaching particularly high concentrations in the intima [Creel et al. 2000; Suzuki et al. 2001]. The concentrations exerting increased TF expression are indeed comparable with local tissue concentrations encountered after stent deployment. Furthermore, the drugs remain detectable for up to 12 weeks after stent deployment in vivo [Vogt et al. 2004]; therefore, the time course of reendothelialization coincides with the presence of the drugs in the vessel wall after stenting.

Hence, these data suggest that both rapamycin and paclitaxel may indeed promote thrombus formation and favor stent thrombosis in vivo not only by an enhanced TF expression, but also by a diminished fibrinolysis, particularly when antithrombotic drugs are withdrawn, or when cytokine levels are elevated, as it occurs in acute coronary syndromes.

**Vasoconstriction after DES deployment**

In addition to these findings, DES, unlike BMS, can impair the endothelial response to acetylcholine- and exercise-mediated vasodilation in vessel segments adjacent to the stent, promoting endothelial dysfunction [Hofma et al. 2006; Togni et al. 2007]. However, underlying atherosclerotic disease in adjacent vessel segments may have contributed to these findings [Nakazawa et al. 2008]. Vasoconstriction alters coronary flow velocity and may thereby further promote thrombotic events; however, clinical consequences of these findings are still uncertain.
FUTURE STENT DESIGN

The optimal DES prevents restenosis and at the same time accelerates reendothelialization. Hence, much effort is made to investigate novel agents for coating DES in addition to improving the polymers as well as the drug-release profile. Promising results have been observed after bioabsorbable drug-eluting stent implantation. Similar rates of restenosis and major adverse cardiac events have been reported after bioabsorbable DES deployment as compared to durable polymer DES [Ormiston et al. 2008]. In the porcine coronary artery stenting model, stents covered with integrin-binding cyclic Arg-Gly-Asp peptides promote reendothelialization by enhancing the recruitment of endothelial progenitor cells [Blindt et al. 2006]. Similar results have been observed after coating stents with antibodies against CD34 to capture endothelial progenitor cells [Aoki et al. 2005]. Titanium-nitride-oxide coated stents diminish platelet adhesion, reduce fibrinogen binding, and decrease rates of restenosis and major adverse cardiac events as compared with BMS [Windecker et al. 2005]. Dimethyl sulfoxide (DMSO) seems to be a promising agent for use on DES as well. DMSO inhibits VSMC proliferation and migration, and, in contrast to rapamycin and paclitaxel, decreases TF expression in endothelial cells, vascular smooth muscle cells, and monocytes; furthermore, intraperitoneal application of DMSO prevents thrombotic occlusion in vivo in a mouse model of photochemical carotid artery injury [Camici et al. 2006]. Cardiac glycosides may represent another candidate drug to be applied on DES as they exert antiproliferative effects on VSMC and at the same time decrease TF expression [Stähli et al. 2007]. However, further studies are needed to evaluate the efficacy and safety of these promising approaches.
CONCLUSIONS

Stent thrombosis is a rare, but severe complication following stent implantation. Early discontinuation of dual antiplatelet therapy has clearly been correlated with an increased risk of stent thrombosis and seems to be a key predictor of thrombotic events. Patient-, lesion-, and procedure-related factors as well as the stent itself are involved in the pathogenesis of stent thrombosis. DES indeed exert prothrombogenic effects as they delay reendothelialization by inhibiting proliferation and migration of endothelial cells, impairing recruitment of endothelial progenitor cells, and enhancing TF expression. Hence, there is good reason for improvement of current DES, not only by developing novel polymers and improving drug release profiles, but also by identifying new drugs suitable for application on stents.
REFERENCES


FIGURE LEGENDS

**Figure 1:** Pathophysiological mechanisms of stent thrombosis after drug-eluting stent (DES) deployment. Procedure-related factors such as stent malapposition predispose to stent thrombosis. Eosinophilic infiltrates around stent struts reflect a hypersensitivity reaction, probably to the polymer, which delays vascular healing. The drugs released from the stent delay reendothelialization by inhibiting proliferation and migration of endothelial cells, impair the function of endothelial progenitor cells, and enhance expression of tissue factor (TF), all of which favor thrombus formation.

**Figure 2:** Rapamycin enhances tissue factor (TF) expression via inhibition of the mammalian target of rapamycin (mTOR), whereas paclitaxel increases TF expression by enhanced c-Jun terminal NH₂ kinase (JNK) activation.
Figure 1
Figure 2