New Drug-Eluting Stent Platforms to Prevent Stent Thrombosis

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Although earlier reports from randomized controlled clinical trials suggested that the incidence of stent thrombosis following drug-eluting stent (DES) implantation was similar to or less than that observed following bare-metal stent deployment, longer-term follow-up has revealed a persistent, protracted risk for thrombosis following DES. This apparent divergence in risk for thrombosis becomes evident beyond 6 to 12 months following deployment. The proposed etiologies of late DES thrombosis are multifactorial and differ somewhat from those factors incriminated in bare-metal stent thrombosis. Prevention strategies are in development to address polymer hypersensitivity/inflammatory response, delayed endothelialization/vessel healing, late incomplete stent apposition, persistence of the underlying endoluminal metal prosthesis, and discontinuation of antiplatelet therapies.

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Thrombosis of a coronary stent—regardless of the time duration elapsed following deployment—represents a catastrophic medical emergency with an associated high (40% to 50%) mortality and morbidity (50% to 70% Q-wave myocardial infarction).[1-3] The multifactorial etiology of stent thrombosis has complicated development of a consensus strategy for its prevention. Indeed, stent thrombosis may result from intrinsic thrombogenicity of

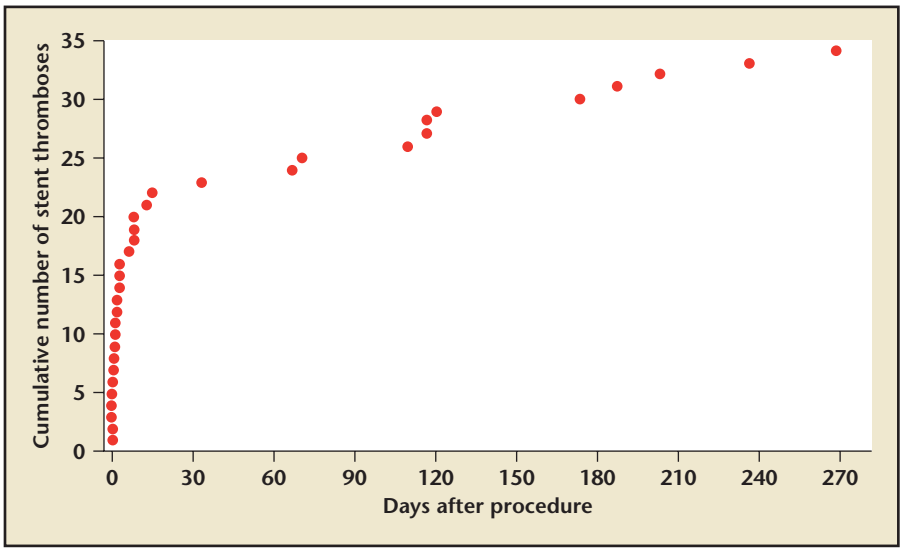


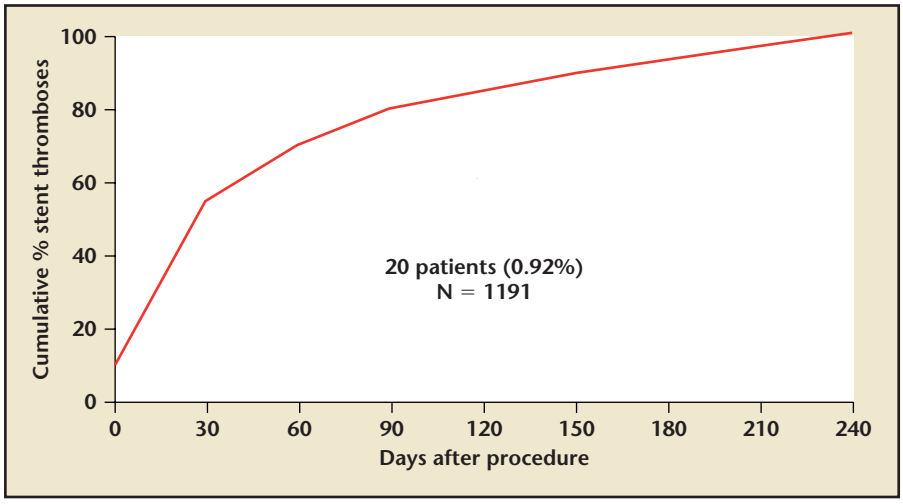
Figure 1. *Isolated cases of stent thrombosis following bare-metal stent deployment occurring beyond 180 days follow-up were observed in the Fuqua Heart Center (Atlanta, GA) experience. Reproduced with permission from Heller LI et al.*[17] www.medreviews.com

the stent prosthesis itself (material, design, surface coating, etc), patient and/or target lesion factors (reference vessel diameter, lesion length, acute coronary syndrome, diabetes, chronic kidney disease, etc), procedure-related factors (suboptimal deployment, incomplete stent expansion, residual stenosis, etc), or a combination of these factors.[4,5]

In the era of bare-metal stent (BMS) deployment, stent thrombosis prevention strategies focused on optimization of stent deployment (high pressure post-dilatation, intravascular ultrasound [IVUS] guidance)[6-8] and on periprocedural and late (30 days to 1 year) adjunctive pharmacotherapies.[9-12] Following BMS deployment, the propensity for stent thrombosis declines over time beyond 30 days and, particularly, after 6 months.[13-16] In a cumulative analysis of 8 clinical series involving almost 20,000 patients undergoing BMS deployment, the average incidence of stent thrombosis through 30-day follow-up was 1.2% (range 0.4% to 2.8%).[4] However, from clinical registry experiences involving longer-term follow-up, isolated episodes of BMS thrombosis continue to be observed out to and beyond 6 months (Figures 1 and 2).[17,18] In one report of acute coronary syndromes associated with the discontinuation of aspirin therapy, 20 patients with an ST-segment elevation myocardial infarction syndrome were described.[19] Of note, 10 out of these 20 patients had BMS thrombosis at an average of 15.5 months following stent deployment and an average of 10 days following aspirin discontinuation. Therefore, although rare, late stent thrombosis has been observed following BMS deployment, particularly after discontinuation of aspirin therapy. Although cases of late BMS thrombosis may have gone unreported due to low frequency occurrence, it is likely that this phenomenon has been responsible for isolated cases of sudden cardiac death and, thus, went undiagnosed.[20]

A difference in the temporal profile for the occurrence of stent thrombosis between BMS and drug-eluting stents (DES) was appreciated only after longer-term follow-up of DES patients and after commercial availability allowed a large number of DES to be implanted (Figure 3). Although earlier reports from randomized controlled clinical trials suggested that the incidence of stent thrombosis following DES was similar to or less than that observed following BMS deployment,[21,22] longer term follow-up has revealed a persistent,

Figure 2. *The Texas Medical Branch (Galveston, TX) experience demonstrates a small percentage of stent thrombosis events occurring at or beyond 6 months following bare-metal stent deployment. Reproduced with permission from Wang F et al.*[18] www.medreviews.com



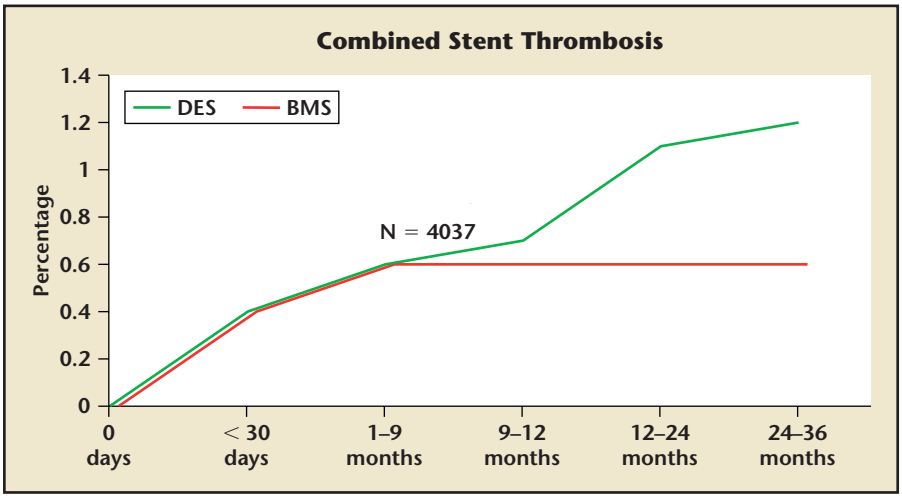


Figure 3. *Cumulative percentage of stent thrombosis following deployment of either BMS or DES over time to 3 years follow-up. A protracted, persistent risk of late stent thrombosis (beyond 6 to 9 months) appears to be present for DES (according to a meta-analysis of all published data). BMS, bare-metal stents; DES, drug-eluting stents.*
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protracted risk for thrombosis following DES.[23,24] This apparent divergence in risk for thrombosis becomes evident beyond 6 to 12 months following deployment. The proposed etiologies of late DES thrombosis are multifactorial and differ somewhat from those factors incriminated in BMS thrombosis (Figure 4). The proposed etiologies for late DES thrombosis for which prevention strategies could be developed include polymer hypersensitivity/inflammatory response, delayed endothelialization/vessel healing, late incomplete stent apposition (ISA), persistence of the underlying endoluminal metal prosthesis, and discontinuation of antiplatelet therapies. Each of these factors will be examined in light of new technologies under development that have been designed to specifically address them and reduce the risk of late DES thrombosis.

Polymer Hypersensitivity/ Inflammation

Hypersensitivity reactions have been described following deployment of the Cypher® sirolimus-eluting stent as well as the Taxus® paclitaxel-eluting stent.[25] Most of these events are systemically manifested as rash, urticaria, asthmatic wheezing, hypotension, etc, and occur early (within weeks) of stent deployment. Late, localized hypersensitivity to the polymer coating has been identified histologically and has been incriminated in both in-stent restenosis and late thrombosis.[26] These observations have prompted the recommendation for "continued efforts to improve polymer biocompatibility."[26] Indeed, marked differences exist between the currently available DES platforms in polymer thickness (Figure 5), visioelastic properties, and polymer surface area exposure to tissue over time. The polymer surface area exposures over time for the durable, biostable polyethylene-co-vinyl acetate–poly n-butyl methacrylate (PEVA-PBMA) (Cypher) and Translute™ (Taxus) are shown in comparison with the reservoir-based bio-resorbable polylactide co-glycolide (PLGA) polymer matrix employed in the CoStar™ DES platform (Figure 6). A marked reduction in polymer surface area exposure is achieved by confining the polymer to laser-drilled reservoirs in a thin strut (0.0035 inch) cobalt chromium stent platform (Figure 7). The rate of polymer matrix degradation and, thus, of drug elution, is determined by the relative ratio of lactic and glycolic acid constituents. The

Figure 4. *Factors etiologic in the occurrence of late thrombosis of DES platforms. DES, drug-eluting stents.*
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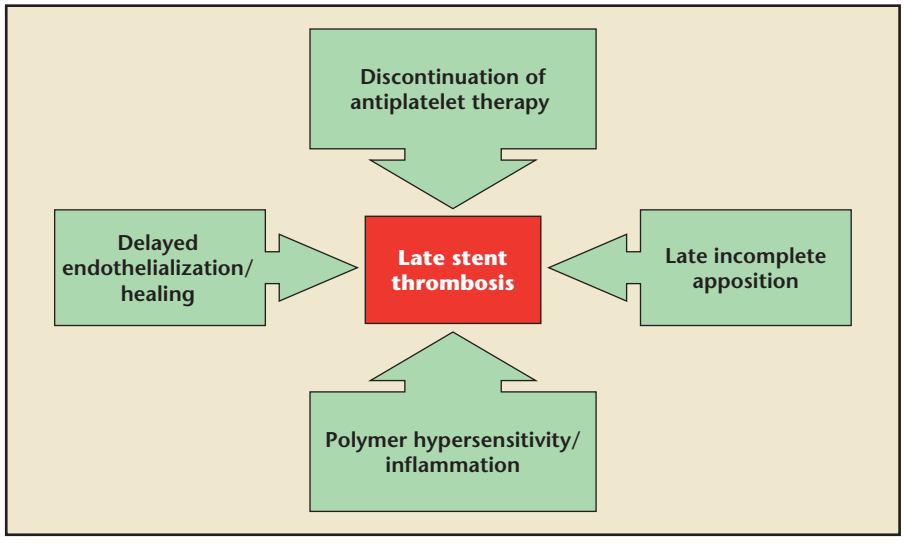


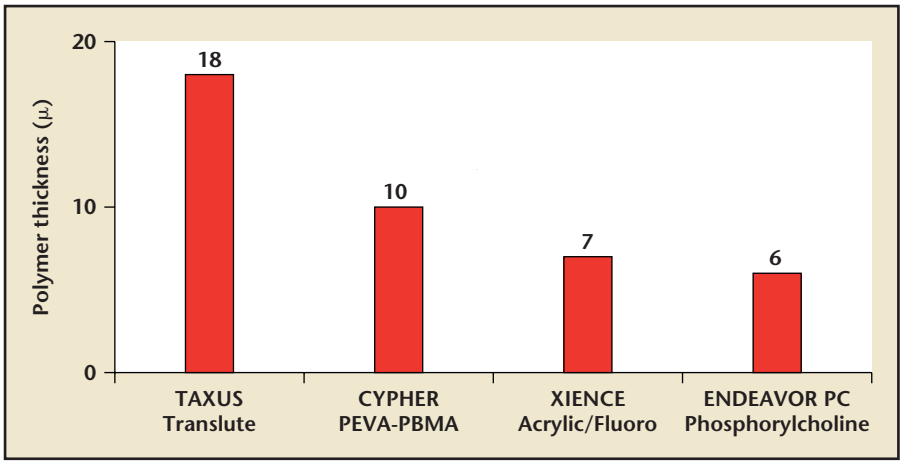


Figure 5. *Relative polymer coating thickness measured on the mural surface of drug-eluting stent platforms that are currently available or in clinical development. These stents incorporate polymer on the luminal surface of the stent as well, although luminal polymer thickness is often less. PEVA-PBMA, polyethylene-co-vinyl acetate–poly n-butyl methacrylate; PC, phosphorylcholine.* www.medreviews.com

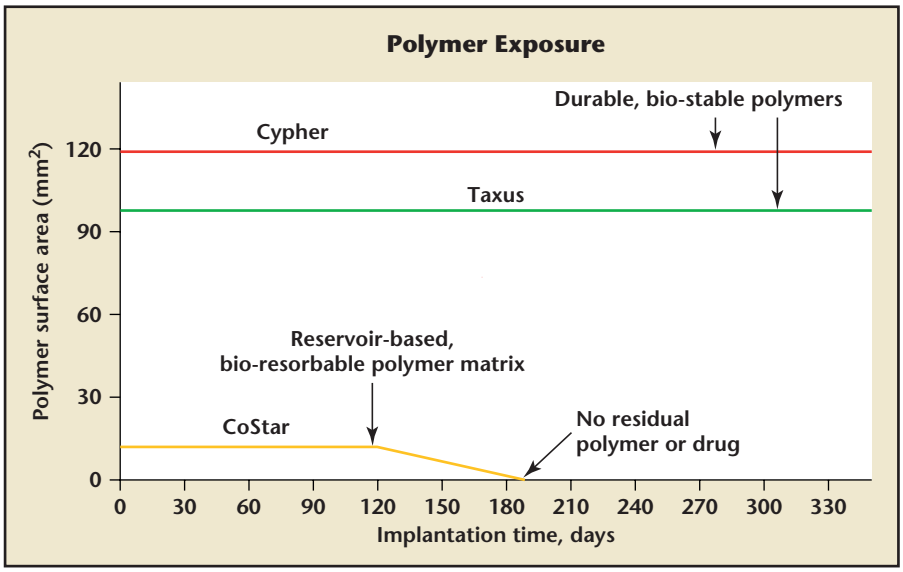
current 85:15 lactic to glycolic acid ratio utilized in the CoStar stent provides complete polymer degradation by 6 months following stent deployment. In over 1000 CoStar coronary stent implantations in 831 patients followed for 12 to 24 months (protocol mandated oral clopidogrel therapy for 6 months), no late stent thromboses have been observed.

An alternative strategy to the use of a biodegradable polymer is the use of a more non-thrombogenic, biocompatible polymer for drug elution, such as phosphorylchlorine (PC). PC is a synthetic copy of the predominate phospholipid that comprises the outer membrane of the red blood cell. Although it is biostable (permanent), by "mimicking" the outer membrane of a red blood cell, PC is biocompatible and thin relative to the other available polymer coatings. PC appeared to be non-thrombogenic and demonstrated significantly less platelet adhesion when compared with a non–PC-coated stent prosthesis in a baboon brachial implant study (Figure 8).[27] PC is employed on the Zomaxx® and Zodiac zotarolimus-eluting DES platforms under development and on the Endeavor® ABT-578–eluting DES platform under development. In more than 1300 patients treated with the Endeavor DES in clinical trials, only 4 total stent thromboses (0.3%) were observed, all of which occurred within 30 days of deployment. No late stent thromboses have yet been reported following Endeavor stent deployment.

Delayed Endothelialization and Vessel Healing

Recent histopathologic studies have incriminated delayed healing and endothelial-stent coverage in late thrombotic risk following DES deployment (Figure 9).[28] In part, the same antiproliferative medication effects that limit the neointimal response to DES deployment also result in delayed healing and resultant limitation in stent coverage by mature endothelial cells. Delayed and/or incomplete healing leaves polymer and metal struts exposed and thus predisposes the patient to thrombotic risk, particularly if dual antiplatelet therapy is discontinued. Specific strategies aimed toward enhanced vessel healing and endothelial cell stent coverage have included both active and passive (stent surface modifications) modalities. One

Figure 6. *Estimated polymer surface area exposure to tissue over time in the porcine model. Surface area exposure for the durable biostable polymers on the currently available Cypher and Taxus drug-eluting stents remains high over time in comparison with the reservoir-based, bioresorbable polymer matrix incorporated into the CoStar stent. The CoStar PLGA bioresorbable polymer undergoes complete biodegradation by 6 months following deployment. PLGA, polylactide co-glycolide.* www.medreviews.com



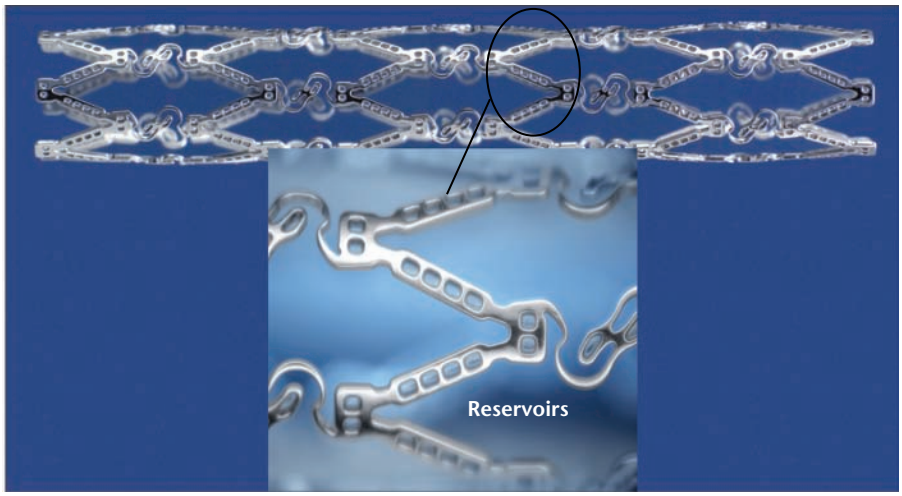
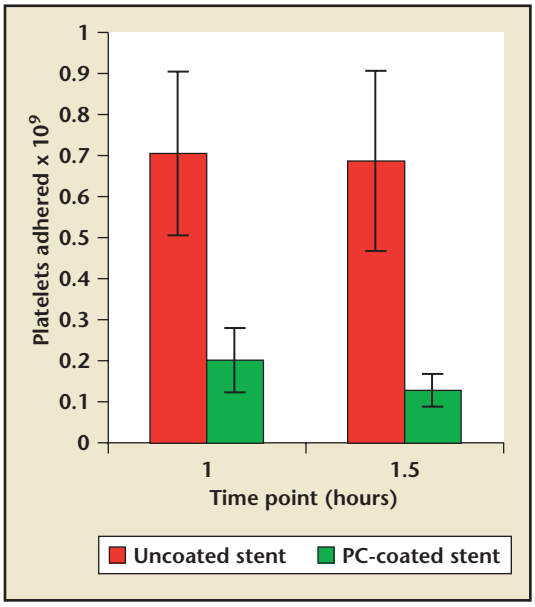


Figure 7. *Laser-drilled polymer reservoirs are located in the thin strut (0.0035 inch) cobalt chromium stent platform. PLGA polymer degradation occurs within 6 months of stent deployment. PLGA, polylactide co-glycolide. Reproduced with permission from Conor Medsystems.* www.medreviews.com

active strategy involves the incorporation of CD34 circulating endothelial progenitor cell (EPC) surface antigen-specific monoclonal antibodies onto the surface of a stent prosthesis. The CD34 antibodies may be incorporated into either a polymer matrix or an expanded polytetrafluoroethylene (PTFE) coating to recruit EPC cell surface attachment to the stent platform, with subsequent accelerated differentiation and maturation (Figure 10). In vivo, EPC capture has been demonstrated following deployment of this novel DES platform. Other active strategies aimed at promoting healing have included elution of 17-β estradiol to reduce the inflammatory response to stent vessel injury and/or to enhance re-endothelialization. 17-β estradiol has been eluted from a PC polymer (BiodivYsio®). In addition, bisphosphonates (liposomal alendronate, liposomal chlodronate) have been incorporated into DES platforms to reduce macrophage infiltration in response to stent vessel injury. The degree of macrophage infiltration in response to stent deployment is the most powerful correlate of subsequent neointimal proliferative response and intimal volume.[29] Bisphosphonates prohibit macrophage activation and markedly reduce the number of macrophages present in the zone of vessel injury.[30] In addition, oxygen free-radical scavengers have been incorporated into DES platforms in an attempt to reduce oxidative damage and to preserve the natural production of nitric oxide (NO). One platform currently in clinical development (the Noblesse Stent) utilizes an oxygen free-radical scavenger covalently bound to a biocompatible poly-ester-amide (PEA) coating on the surface of a metal alloy prosthesis, which functions as a superoxide "biofilter" to retire oxygen-free radicals derived from oxidative phosphorylation and/or lipid peroxidation. A potential advantage of a PEA-NO preserver conjugated drug releaser from a biodegradable polymer is that it provides controlled, prolonged release of a non-toxic stimulus to activate natural defense mechanisms with no subsequent long-term residua of the drug or polymer. In addition, arginine-glycine-aspartate (RGD) peptides have been incorporated into DES platforms to reduce inflammation and promote healing. Finally, "dual drug" stent platforms have been developed, which incorporate an anti-inflammatory medication in conjunction with an anti-proliferative agent. These devices include the Symbio™, which elutes paclitaxel

Figure 8. *Comparison of platelet adhesion to phosphorylcholine (PC)-coated and uncoated bare-metal stent platforms in a baboon brachial implant study. Fewer platelets are adherent to the PC-coated platform. Adapted from Lewis AL.*[27] www.medreviews.com



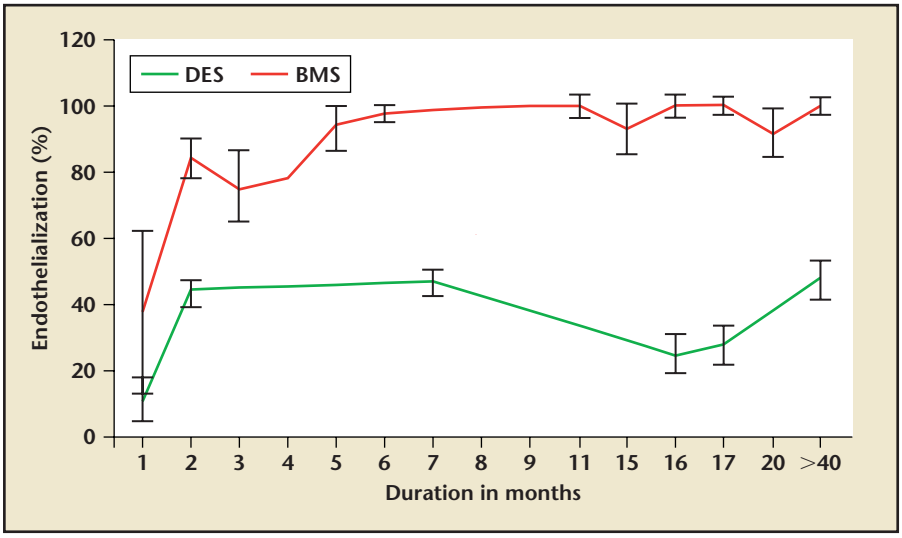


Figure 9. *Pathology of DES in man as derived from post-mortem histopathologic study. DES demonstrate delayed healing and reduced percent endothelial cell coverage when compared with BMS. Delayed healing and reduced endothelial cell coverage may contribute to late thrombotic risk. DES, drug-eluting stents; BMS, bare-metal stents. Reprinted with permission from Joner M et al.*[28] www.medreviews.com

and pimecrolimus; the Zodiac, which elutes zotarolimus and dexamethasone; and the Clever stent, which elutes everolimus and clobetasol. The Symbio stent is being evaluated in a European clinical trial (the GENESIS trial).

Passive strategies to enhance healing and endothelial coverage include stent surface modifications, such as use of a microporous material. These textured surfaces can be loaded with medication and also stimulate endothelial cell migration. One such platform, the Yukon® Choice DES, incorporates a microporous surface that can be drug-loaded prior to stent deployment and subsequently elutes medication over approximately 25 days. This device has been loaded with rapamycin and compared in a randomized controlled trial (A Randomized Trial of a Non-polymer-Based Rapamycin-Eluting Stent Versus a Polymer-Based Paclitaxel-Eluting Stent for the Prevention of Restenosis [ISAR-TEST]) with the Taxus paclitaxel-eluting stent, which employs a biostable polymer for drug elution. In this small but randomized comparison, the Yukon Choice DES was not inferior to the Taxus stent.[31] Additional stent surface modifications to passively promote healing and endothelial coverage involve nanotechnology and other texturing strategies.

Late Incomplete Stent Apposition

Late ISA has been described following intravascular brachytherapy, with both BMS and DES.[32-35] When systematic IVUS is performed post-DES deployment and in late follow-up, approximately 5% to 7% of patients demonstrate persistent ISA (present on both the initial and late IVUS studies), while about 5% of patients demonstrate late-acquired ISA that is not evident on the initial exam.[8,36-38] Late ISA is most frequently located at the body of the stent and appears to be related to regional vessel positive remodeling.[36] Although the initial reports of late ISA following DES deployment suggested a benign course to 1 year of follow-up,[39,40] more recent observations have incriminated late ISA as a possible etiology in isolated cases of DES thrombosis.[36,41] As late ISA has been described in up to 5% of cases following BMS deployment,[35] it is unclear whether this phenomenon confers any increased risk for stent thrombosis following DES compared with BMS. Nevertheless, these observations and concerns underlie the premise that acceptance of "a mild degree of in-stent neointimal proliferation that is still compatible with a good clinical outcome might offer a reasonable compromise between safety and efficacy," while we await the development of DES with both

Figure 10. *EPC capture on the stent prosthetic surface is achieved by incorporation of specific monoclonal anti-CD34 cell surface antigen antibodies. Successful EPC capture with subsequent EPC differentiation and maturation has been demonstrated in vivo. EPC, endothelial progenitor cell.*
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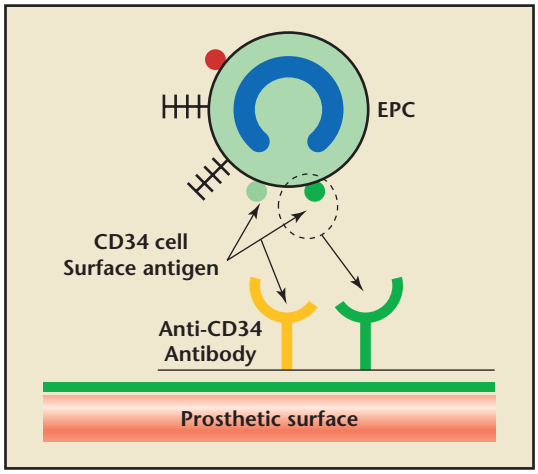


antiproliferative and pro-healing properties.[42] In this context, the Endeavor ABT-578–eluting DES with PC polymer coating has been associated with a greater degree of in-stent late lumen loss (0.61 mm vs 0.17 mm in the Cypher/SIRIUS trial and 0.39 mm in the Taxus/TAXUS IV trial) and more uniform neointimal stent strut coverage. Of note, no stent thromboses have been observed beyond 30 days in late follow-up from 1 to 3 years in over 1300 patients after Endeavor stent deployment (total stent thrombosis rate 4 out of 1300; 0.3%).[42] Thus, a delicate balance between "enough" neointima to provide protective coverage and "not too much" to preclude significant angiographic/clinical restenotic benefit may exist. Other IVUS-derived measurements at the time of DES deployment that have been correlated with subsequent (≤6 months) stent thrombosis include incomplete stent expansion, reduced minimum stent cross-section area, and the presence of a significant residual stenosis in the target vessel.[8,43] The use of IVUS guidance to optimize DES deployment and, thus, to minimize the risk of stent thrombosis, appears to be increasing.

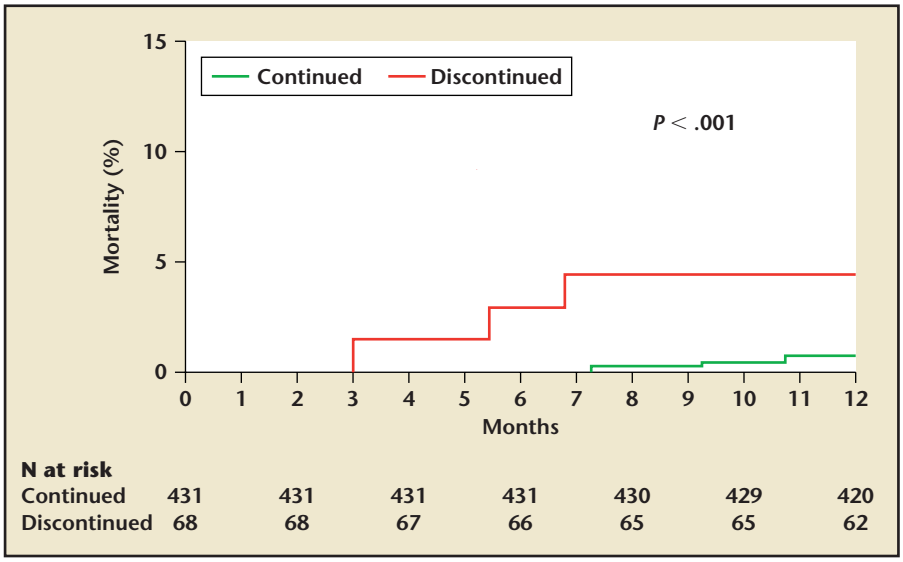
Incorporation of Adjunctive Antithrombotic Agents

Significant interest exists in the use of non-thrombogenic surface coatings or polymers in addition to the incorporation of adjunctive antithrombotic agents. As noted previously, the PC polymer coating appears to be non-thrombogenic and associated with a lesser degree of platelet deposition.[27] Similarly, historical precedence supports the potential utility of covalent heparin bonding to the stent platform to prevent thrombosis.[44-47] The cumulative clinical trial and registry experience with the Hepacoat stent® (unfractionated heparin bonding) demonstrates a very low incidence of stent thrombosis (0.1% to 0.7%) depending on the clinical syndrome (presence or absence of ST-elevation myocardial infarction).[44-46] Others have incorporated platelet glycoprotein IIb/IIIa receptor inhibitors (abciximab, eptifibatide) onto stent platforms.[48-50] Interestingly, the incorporation of abciximab onto a BMS platform was associated with both a low frequency of stent thrombosis and a significant reduction in late lumen loss in stent, angiographic, and clinical restenosis.[49,50] Finally, incorporation of direct-acting antithrombin agents, such as bivalirudin, onto DES platforms has been suggested. Whether or not any of these strategies can match the durable and efficacious presence that is offered when the antithrombotic agent is disposed upon the stent remains to be determined.

Discontinuation of Oral Antiplatelet Therapies

Early (≤30 days) discontinuation of clopidogrel therapy following DES deployment has been associated with diminished survival to 1 year (Figure 11).[51] Furthermore, several clinical series of DES-treated patients from which correlates of angiographic stent thrombosis have been determined have demonstrated a significant risk for stent thrombosis when premature discontinuation of antiplatelet therapy occurs.[52,53] However, a closer analysis of the population attributable risk percent undertaken to more accurately discern the proportion of stent thromboses that is actually due to the discontinuation of clopidogrel showed that the majority of stent thromboses (68% to 85%) are attributable to other factors.[54] Although clopidogrel discontinuation unquestionably plays a critical role in many instances of stent thrombosis (especially early thrombosis), many other factors contribute and

Figure 11. *Early (≤30 days) discontinuation of thienopyridine therapy following drug-eluting stent deployment during ST-segment elevation myocardial infarction is associated with a significant increase in mortality during clinical follow-up to 1 year. Early thienopyridine discontinuation was common (occurring in about 1 out of every 7 patients) and was associated with increased mortality beyond 3 months follow-up. Reprinted with permission from Spertus JA et al.*[51] www.medreviews.com



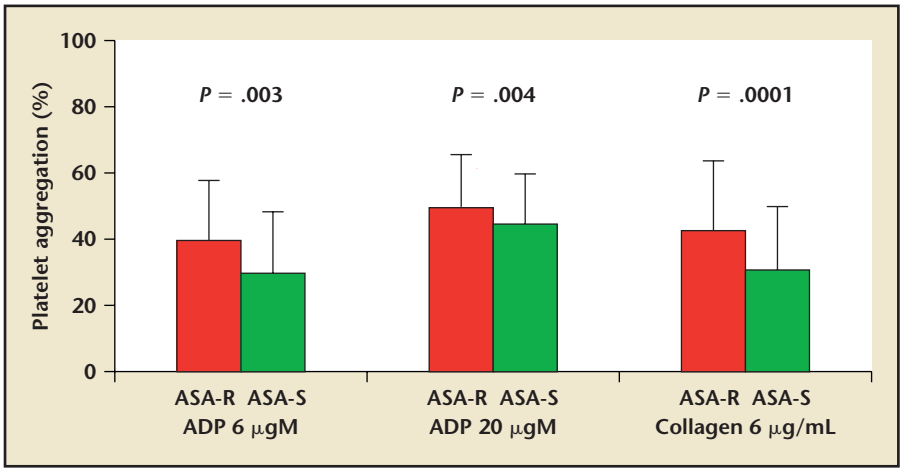


Figure 12. *Platelet aggregation stratified by aspirin resistance in patients on concomitant clopidogrel therapy. ASA-R patients have increased platelet aggregation (less inhibition), despite concomitant clopidogrel therapy, than do patients who are ASA-S. Thus, patients who are ASA-R demonstrate a diminished response to clopidogrel platelet inhibition. ASA-R, aspirin resistant; ASA-S, aspirin sensitive; ADP, adenosine diphosphate. Reprinted with permission from Angiolillo DJ et al.*[59] www.medreviews.com

must be addressed. In addition to the issues of delayed healing, ISA, and polymer hypersensitivity discussed previously, factors such as clopidogrel and/or aspirin resistance may contribute as well.[55-58] Patients who experienced DES thrombosis appear to cluster at or above the 75% percentile for residual platelet aggregation following clopidogrel treatment.[57] In addition, resistance to aspirin has been correlated with increased risk for stent thrombosis.[58] Interestingly, patients who are resistant to aspirin also demonstrate a blunted or diminished responsiveness to clopidogrel, raising the prospect of a "hyporesponsive phenotype" to currently available oral platelet inhibitor therapies (Figure 12).[59,60] Several "next generation" $P2Y_{12}$ receptor inhibitors that are currently in clinical testing (prasugrel, AZD6140) demonstrate a more rapid onset and greater magnitude of platelet inhibition as well as less inter-individual variability in platelet inhibition than has been observed following clopidogrel.[61] Furthermore, patients who are nonresponsive to clopidogrel are almost invariably responsive to prasugrel.[61] Finally, the very rapidly acting parenteral $P2Y_{12}$ receptor antagonist, cangrelor, or the competitive/reversibly binding AZD6140, which is administered on a twice-daily oral dosing regimen, could possibly be used to "bridge" a patient prior to and following a surgical procedure to minimize the potential thrombotic risk of $P2Y_{12}$ inhibitor discontinuation.

Conclusion

Late stent thrombosis (beyond 6 months to 1 year) following DES deployment has been recognized to have an increased frequency as compared with that exhibited during the historical experience of BMS deployment. It has been the cause of considerable recent concern. Late DES thrombosis is most often unpredictable and yet catastrophic with respect to morbidity and mortality. These observations have prompted considerable interest in the development of new DES platforms that incorporate strategies aimed at reduction of risk for stent thrombosis. Such strategies have included enhanced biocompatibility and/or biodegradability of polymers, incorporation of agents/factors to promote healing and/or endothelial stent coverage, complete biodegradation of the stent platform itself, and incorporation of adjuvant antithrombotic agents. In addition, more effective and, it is hoped, safer options for oral antiplatelet therapy are currently in clinical testing and will become available. ■

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Main Points

- A marked reduction in polymer surface area exposure is achieved by confining the polymer to laser-drilled reservoirs in a thin strut (0.0035 inch) cobalt chromium stent platform.
- An active strategy aimed toward enhanced vessel healing and endothelial cell stent coverage involves the incorporation of CD34 circulating endothelial progenitor cell surface antigen-specific monoclonal antibodies onto the surface of a stent prosthesis. Passive strategies include stent surface modifications, such as use of a microporous material.
- A stent with a phosphorylchlorine polymer coating has been associated with a greater degree of in-stent late lumen loss and more uniform neointimal stent strut coverage.
- Historical precedence supports the potential utility of covalent heparin bonding to the stent platform to prevent thrombosis.
- Patients who are resistant to aspirin also demonstrate a blunted or diminished responsiveness to clopidogrel, raising the prospect of a "hyporesponsive phenotype" to currently available oral platelet inhibitor therapies.

stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45:995-998.
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