Neointimal Formation Following Drug-Eluting Stents: Physiology, Timeline, and the Influence of Drug Delivery Systems

John J. Young, MD, FACC, FAHA, FSCAI

Swedish Heart & Vascular Institute, Seattle, WA

Percutaneous coronary intervention with drug-eluting stents (DES) is currently the preferred approach to the treatment of obstructive coronary artery disease. Large, randomized trials have demonstrated a significant reduction in the incidence of restenosis and the need for target vessel revascularization following implantation of DES compared with bare-metal stents. Follow-up data extending out to 2 to 4 years have demonstrated efficacy in maintaining luminal patency, but recent concerns regarding potential late adverse effects with DES have been raised. These include aneurysm formation and hypersensitivity reactions, as well as subacute and late stent thrombosis requiring compliance with antiplatelet therapy for protracted periods of time. Evolving strategies to mitigate late adverse events with DES include acceleration of endothelialization, gene therapy targeting pro-healing pathways (ie, nitric oxide donors), smooth muscle cell growth inhibitors, bioabsorbable metal and polymeric stents, and concurrent use of local as well as systemic chemotherapy.

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Mechanistic insights gained over the last 2 decades have reshaped our current understanding regarding the pathogenesis of atherosclerosis. Activated immune and inflammatory cells interact with dysfunctional endothelium to cause the retention of oxidized or enzymatically degraded lipid molecules within the subendothelial space.[1] Scavenger receptors on monocytes and macrophages facilitate the uptake of oxidized-low-density lipoprotein,

resulting in the formation of foam cells. Growth factors lead to the proliferation of smooth muscle cells (SMCs) and their migration into the intima, culminating in the characteristic atherosclerotic plaque.[2] Until recently, the prevailing clinical perception of atherosclerotic disease was that of advancing luminal stenosis, with less attention paid to the characteristics of the vessel wall. Over the last decade, however, the emphasis has shifted to the instability of the underlying plaque as the key precipitating factor involved in the pathogenesis of acute coronary syndromes. The therapeutic approach to coronary artery disease has evolved in close conjunction with these insights.

The introduction of balloon angioplasty ushered in the era of percutaneous revascularization. However, abrupt vessel closure and recoil of the treated arterial segment limited the acute and long-term durability of this technique. The development of bare-metal stents (BMS) significantly reduced the acute mechanical limitations of balloon angioplasty, and the addition of antiplatelet strategies decreased the associated short-term thrombotic risk. The resultant effect was successful percutaneous coronary intervention (PCI) with good short-term outcome; however, the vexing problem of restenosis over the intermediate to long-term (6 to 12 months) follow-up remained unsolved.[3] Drug-eluting stents (DES) have evolved that address not only the acute mechanical issues associated with PCI, but more importantly the "Achilles' heel" of restenosis following stent implantation; they also reduce the need for repeat intervention. The success of DES has now been somewhat tempered by the demonstration of late stent thrombotic events, prompting scrutiny of the long-term safety of these devices. The widespread adoption of DES technology into interventional cardiology has raised a number of important questions regarding our understanding of the pathophysiology of acute vessel injury, restenosis, and normal vessel healing.

Restenosis: Pathobiology

Much of what is known about restenosis and neointimal formation comes from intense study of animal injury models and comparison with human material, usually derived from autopsy.[4,5] Restenosis in animal models results from controlled injury induced in normal vessels that subsequently form thick neointima and undergo shrinkage (remodeling) due to scar formation. Early understanding of balloon angioplasty suggested that atherosclerotic plaque was compressed or stretched—concepts that eventually yielded a more comprehensive understanding that both plaque and the normal artery are severely fractured during PCI. Many parallels emerged between human restenosis and animal model counterparts, and these studies assumed a central role in understanding coronary artery injury and healing. Specifically, the porcine coronary models using injuries caused by either stenting or overstretching are now accepted standards by which potential restenosis therapies are studied.[5]

Fundamentally, mature neointima is consistent with a repaired artery and, thus, is desirable. Deeper arterial wall injury following stent deployment in the porcine model results in more exuberant neointima.[5] This observation was subsequently validated and led to improvement in stent designs, with less associated arterial injury.[6] Other stent concepts have attempted to limit injury, but if properly dilated, a 90% stenosis undergoes a 10-fold expansion that induces significant arterial injury associated with thrombus formation, inflammatory and other cellular migration, and proliferation that leads to neointimal hyperplasia. DES also induce such an arterial injury and therefore rely on local drug effects to moderate the neointimal response. Based on these animal studies and on human coronary artery findings, restenosis can be broadly divided into 4 stages (Table 1).[5]

The initial consequences immediately after stent placement are deendothelialization, crush of the plaque, and stretch of the entire artery.[5,7,8] A layer of platelets and fibrin is then deposited at the injured site (*thrombus phase*). Activated platelets through surface expression of adhesion molecules attach to circulating leukocytes and begin a process of rolling along the injured surface. Migration of leukocytes across the

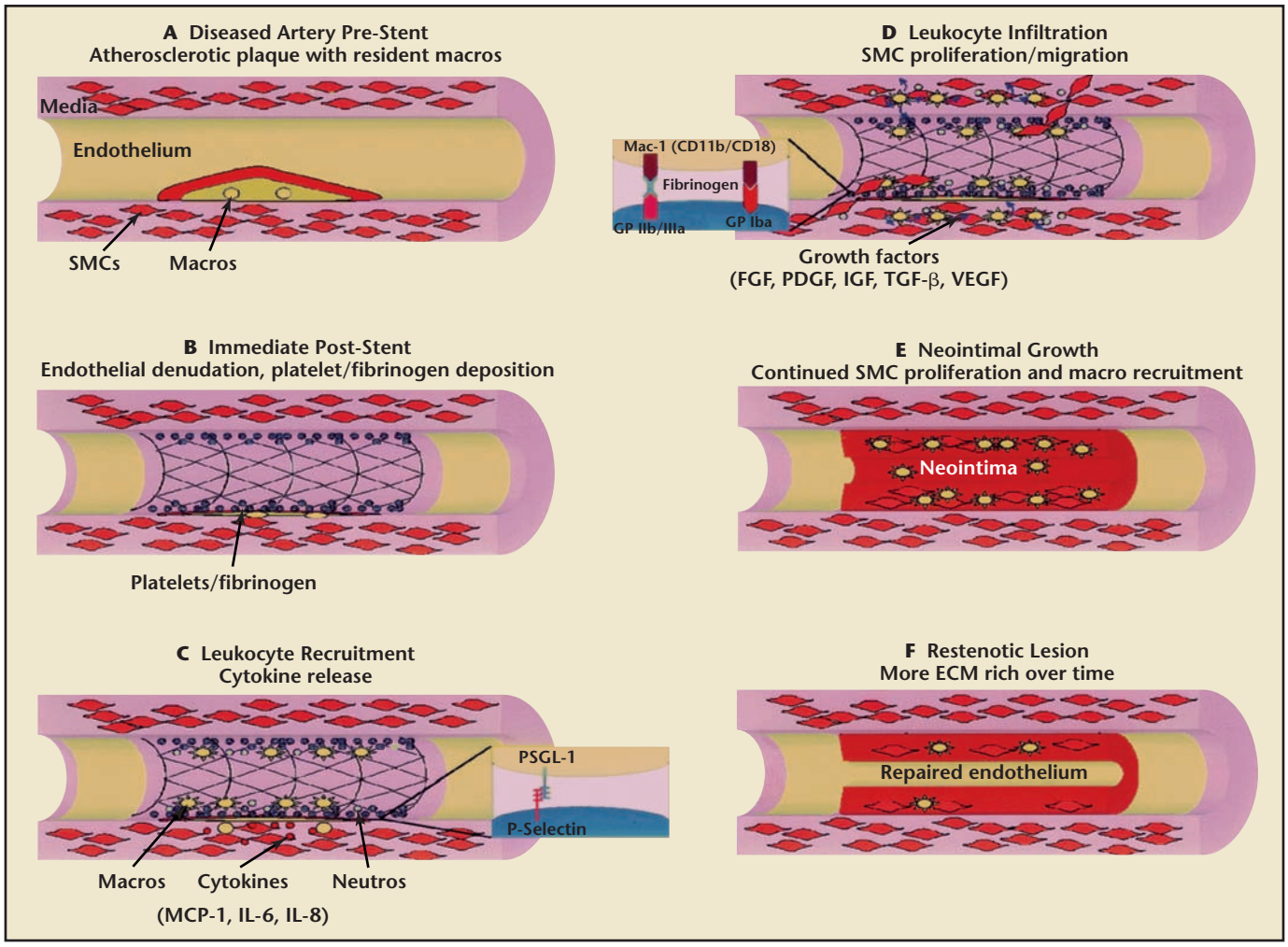
Table 1
Time Course Comparison of Events in Porcine and Human Coronary Stenting

	Porcine Coronary Model	Human Stent Implantation
Thrombus	0-14 days	0-30 days
Inflammation	1-14 days	0-30 days
Endothelialization and granulation tissue	4-16 days	14-90 days
Smooth muscle cells and matrix formation	14-28 days	2-6 months

platelet-fibrin layer and diapedesis into the tissue is driven by chemokines released from SMCs and resident macrophages (*inflammation phase*).[7,8] Growth factors are subsequently released from platelets, leukocytes, and SMCs that stimulate migration of SMCs from the media into the neointima (*granulation phase*). Cellular division takes place in this phase, which appears to be essential for the subsequent development of restenosis.[7,8] Over longer periods of time, the artery enters a phase of remodeling involving extracellular matrix (ECM) protein degradation and resynthesis (*matrix formation phase*). ECM is composed of various collagen subtypes and proteoglycans and constitutes the major component of the mature restenotic plaque. An integrated schematic of restenosis is shown in Figure 1.[8]

Restenosis therefore may be considered to be an uncontrolled and rapid response to tissue injury, characterized by marked intimal growth, SMC proliferation and migration, and the accumulation of macrophages and chronic inflammatory cells. Growth of the neointima is influenced by inflammatory cytokines, the assembly of ECM proteins, and the proliferative response of SMCs to arterial injury. Understanding of these molecular signals, particularly for cell cycle regulation, provided the rationale to test agents with potential anti-inflammatory, cytostatic, or

Figure 1. *Schematic of an integrated cascade of restenosis. Atherosclerotic vessel before intervention* **(A)**. *Immediate result of stent placement with endothelial denudation and platelet/fibrinogen deposition* **(B)**. *Leukocyte recruitment, infiltration, and SMC proliferation and migration in the days after injury* **(C and D)**. *Neointimal thickening in the weeks after injury, with continued SMC proliferation and monocyte recruitment* **(E)**. *Long-term (weeks to months) change from a predominantly cellular to a less cellular and more ECM-rich plaque* **(F)**. *SMC, smooth muscle cell; GP, glycoprotein; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; IGF, insulin-like growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor; MCP, monocyte chemoattractant protein; IL, interleukin; PSGL, P-selectin glycoprotein ligand; ECM, extracellular matrix. Reprinted with permission from Welt FG and Rogers C.*[8] www.medreviews.com



cytotoxic activity for anti-restenotic properties.

Rapamycin/Sirolimus

Rapamycin (sirolimus) is a natural macrocyclic lactone with potent immunosuppressive properties. It has been used in the treatment of renal transplant rejection, and other analogs are presently being evaluated in experimental and clinical studies for their anti-restenotic effects. Rapamycin is a pro-drug that binds to a specific cytosolic protein, FK506-binding protein (FKBP)12, which is upregulated in human neointimal SMCs.[7,9] The FKBP12/rapamycin complex binds to a specific cell cycle regulatory protein, mTOR (mammalian target of rapamycin), and inhibits its activation. TOR is a protein kinase regulatory protein that is involved in critical steps of the cell cycle, including checkpoints that govern DNA damage and repair.[9] mTOR is involved in the transition between the G_1 and S phase, where DNA replication occurs, thus leading to irreversible commitment toward cell division. Rapamycin has been shown to have a cytostatic effect and to induce cell cycle arrest in late G_1 phase. Sirolimus has been shown to inhibit all phases of the restenosis cascade.[7,10] In the porcine model of restenosis, sirolimus-eluting stents markedly reduced the degree of inflammation that correlated with a reduction in neointimal hyperplasia.[10] Furthermore, sirolimus inhibits SMC migration and promotes a contractile, rather than a proliferative, phenotype.[11] These effective results on restenosis have been replicated in various animal studies as well as in clinical trials demonstrating a significant reduction in late loss and the need for target vessel revascularization (TVR).[12,13]

Taxanes/Paclitaxel

Paclitaxel is a diterpenoid compound that contains a complex 8-member taxane ring as its nucleus. The side chain linked to the taxane ring at carbon 13 is essential for its antitumor activity.[7] Paclitaxel exhibits unique pharmacological action as an inhibitor of mitosis by binding to a site on β-tubulin and promoting microtubule formation.[14] Microtubules form the mitotic spindle during cell division and are important in other cellular functions including maintenance of cell shape, motility, and intracellular transport. Paclitaxel binds specifically to the β-tubulin subunit of microtubules and appears to antagonize the disassembly of this key cytoskeletal protein, causing the bundles of microtubules to accumulate in the mitotic phase of the cell cycle and arrest in mitosis (G_2/M phase).[7] Studies of paclitaxel-eluting stents in porcine arteries demonstrated reduction in neointimal and medial cell proliferation.[15] Clinical studies with paclitaxel-eluting stents have also demonstrated effective reduction in restenosis and TVR.[16,17]

Restenosis and Neointimal Formation Following DES

After the initial US Food and Drug Administration (FDA) approval in April 2003, DES have rapidly replaced BMS as the preferred treatment in over 80% of PCI procedures. The majority of the safety and efficacy data that led to approval of DES has been derived from well-defined lesion and population subsets. Concerns about the safety of liberal use in complicated lesions and unselected patient populations have been raised. Even with recent randomized trial data beginning to demonstrate efficacy of DES in complicated lesions (left main disease, multivessel disease, ST-segment elevation myocardial infarction, restenotic lesions, small vessel disease, and chronic total occlusions), the duration of follow-up from these trials is currently limited and the recent concern regarding late stent thrombosis (LST) from earlier studies with long-term follow-up has prompted caution. The efficacy of DES platforms in controlling the intimal proliferation characteristic of restenosis has been well validated; however, the long-term safety of these devices requires careful consideration.

The biological effects of any pharmacological agent delivered locally are influenced by local transport forces, which are related to the properties of the target tissue.[7,18] The highly heterogeneous composition of the arterial wall and its asymmetric geometry represents a challenge for most agents applied in DES technologies. The ideal compound for intramural delivery should contain hydrophobic elements to ensure high local concentrations as well as hydrophilic properties to allow homogeneous drug diffusion. Altered transport of these agents through the vessel wall may lead to both toxic levels in areas where the drug may accumulate and nontherapeutic levels in remote regions away from the drug reservoir. In a bovine carotid model, rapamycin and paclitaxel show markedly different profiles of transmural distribution, with rapamycin distributing evenly through the artery, whereas paclitaxel remains primarily in the subintimal space.[19] In addition, thrombus apposed on stents creates large variations in drug uptake and can act to either increase or decrease wall deposition according to clot and stent geometry.[20] These effects of stent positioning and local transport mechanisms become increasingly important as these devices (DES) deliver specific therapeutic agents compared to historical devices that provided only mechanical support (BMS).

Our understanding of the mechanisms of DES failure is still limited. It appears that the causes of restenosis after implantation of BMS and DES are fundamentally the same. The relative contributions of individual factors to the development of restenosis, however, appear to differ considerably between DES and BMS. The magnitude of the biological response of DES on neointimal proliferation has likely unmasked 2 other aspects of restenosis after BMS: 1) mechanical-related failures (stent underexpansion, plaque prolapse) and 2) technique-related factors (barotrauma, geographic miss). Although DES have drastically reduced angiographic and clinical restenosis across a broad patient cohort, certain patient and lesion characteristics contribute to the success or subsequent failure of the treatment.[21] Further risk stratification based on patient and lesion characteristics combined with an optimal deployment technique may result in improved clinical outcome.

Endothelial integrity is essential for maintaining vascular homeostasis, and endothelial denudation results in intimal thickening. Endothelial dysfunction may persist for months following vascular injury and is more pronounced with BMS as compared with balloon angioplasty.[22] Whether the development of a functional endothelial layer is further delayed after DES implantation remains to be defined. A recent registry consisting of 40 cadavers studied at autopsy of patients who had previously been treated with DES or BMS demonstrated a decrease in percent endothelialization (DES compared to BMS) out to 40 months of follow-up (Figure 2).[23] The major pathologic finding distinguishing thrombosed from patent DES was evidence of greater delay in arterial healing as manifested by persistent fibrin deposition and reduced endothelial coverage. In addition, Kotani and colleagues[24] recently reported angioscopic data from 37 consecutive PCI procedures (15 DES and 22 BMS) in 25 patients at 3- to 6-month follow-up, with a focus on neointimal coverage of stent struts and existence of thrombi. Thrombi were more common in stents with incomplete neointimal coverage, and the degree of endothelialization was less complete in the DES patients (Figure 3).[24] Animal studies have also identified sites of DES overlap to be associated with delayed arterial healing and inflammation,[25] whereas human clinical trials involving DES overlap have reported variable results.[26]

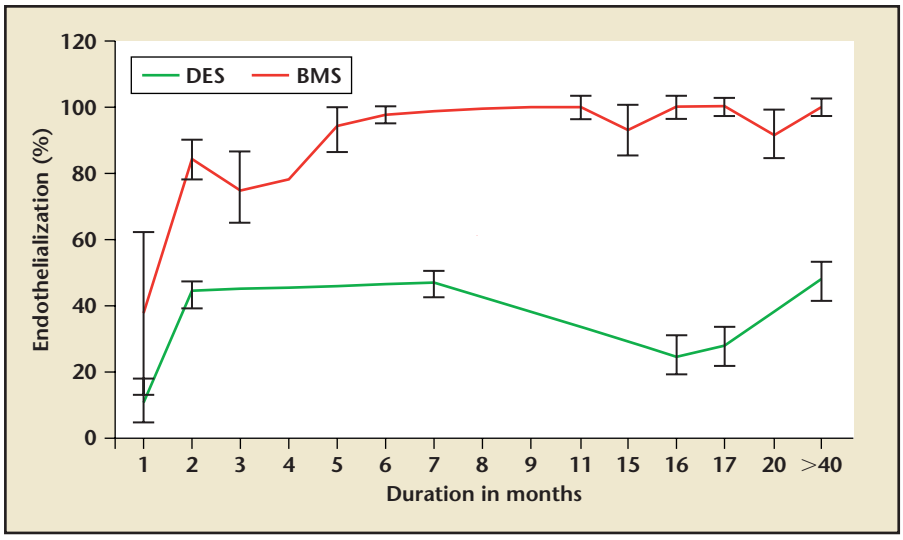


Figure 2. *Line chart comparing the percentage of endothelialization in DES versus BMS as a function of time. DES (green line) consistently show less endothelialization compared with BMS (red line), regardless of time point. Even beyond 40 months, DES are not fully endothelialized, whereas BMS are completely covered by 6 to 7 months. DES, drug-eluting stents; BMS, bare-metal stents. Reprinted with permission from Joner M et al.*[23] www.medreviews.com

The most important contributing factor to date for drug-eluting stent late stent thrombosis has been the premature discontinuation of dual antiplatelet therapy.

Although the risk of LST following DES appears to be small (0.35% to 0.6%), the associated mortality for patients suffering DES LST can be as high as 45% to 50%.[27-31] Predictors of DES LST include stenting across ostia of branch points, bifurcations, previous sites of brachytherapy and highly necrotic plaques, as well as proximal or distal plaque disruption with stent implantation.[27-32] In addition, diabetes mellitus, renal failure, and lower left ventricular ejection fraction have been associated with LST. The most important contributing factor to date for DES LST has been the premature discontinuation of dual antiplatelet therapy. Several studies, including a 19-center study of myocardial infarction patients, have demonstrated the important link between premature thienopyridine discontinuation and the risk of DES LST and mortality.[33] A recent observational study of 4666 consecutive PCI patients (3165 BMS, 1501 DES) who were event-free at 6-month follow-up stratified patients by stent type (DES or BMS) and self-reported clopidogrel use at 6 and 12 months.[34] Although there was no

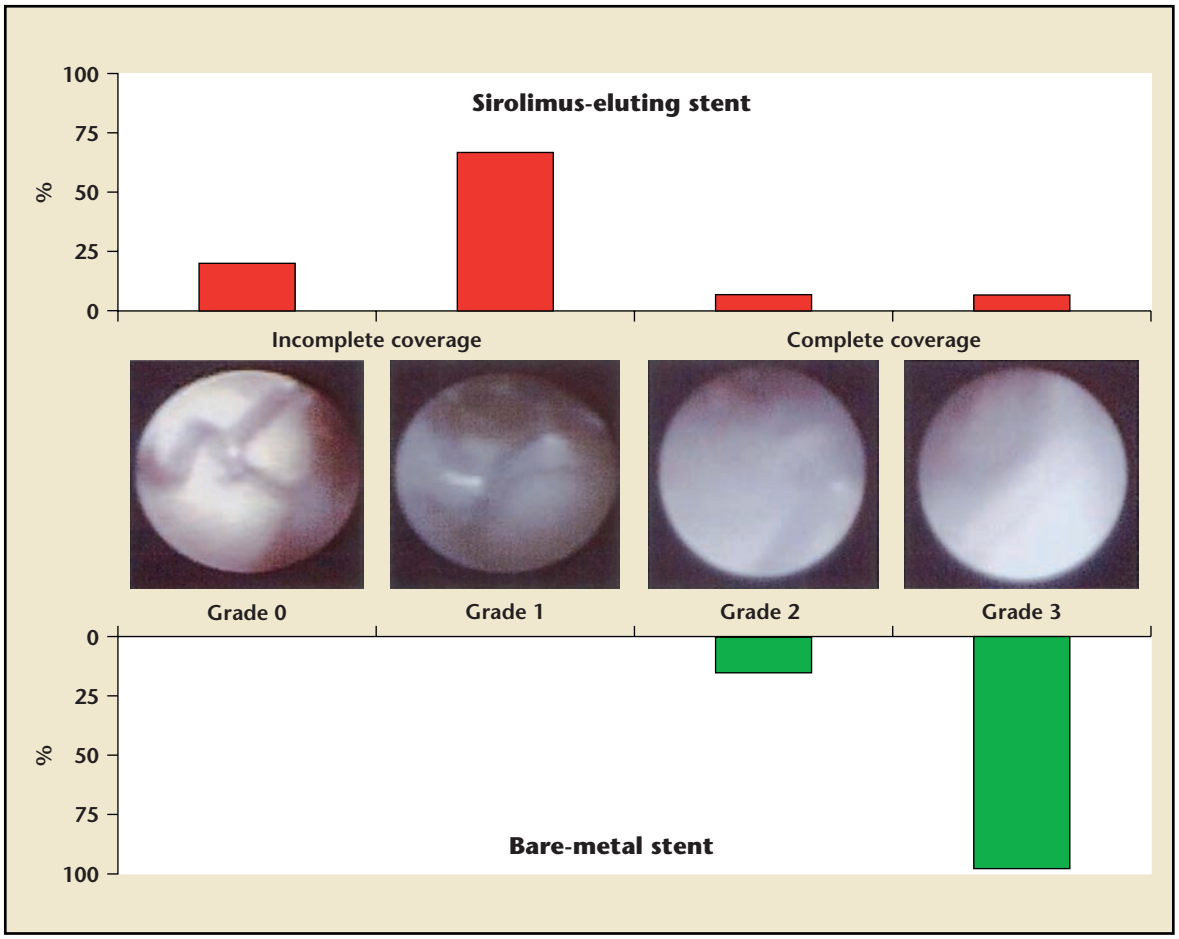


Figure 3. *Angioscopic images show the grading for neointimal stent strut coverage. Neointimal coverage was more complete with bare-metal stents compared with sirolimus-eluting stents (P < .0001). Reprinted with permission from Kotani JI et al.*[24] www.medreviews.com

significant difference in clinical outcomes by clopidogrel use at 24-month follow-up in the BMS group, the DES group demonstrated a significant reduction in the risk of death or myocardial infarction with extended (6 to 12 months) clopidogrel use. These results combined with previous studies suggest that all patients with DES should continue to take clopidogrel for at least 12 months after PCI.

DES LST is likely multifactorial in causality. Although the degree of endothelialization/delayed healing is likely to contribute in certain subsets of patients, this phenomenon is dependent both on patient factors and technical factors. Additional factors may contribute to local arterial hypersensitivity reactions, as well as to the unusual vessel response (substantial vessel positive remodeling with acquired stent malapposition) reported in a few patients.[35,36] Each DES platform may elicit unique arterial responses due to different drugs and polymer carriers interacting with unique local biology within a given patient. Future platforms and therapies will need to incorporate evolving molecular and cellular mechanisms to provide the optimal treatment response.

Future Strategies

Evolving strategies to achieve restoration of normally functioning endothelium following PCI revolve around improvements in DES deployment technique, bioabsorbable stents, therapies based on genes and stem cells, pharmacotherapy combinations, and supplementation with growth factors.

The approach of direct stenting without balloon predilation was found to cause less endothelial injury, rapid restoration of the endothelial layer, and less intimal thickening in rabbit arteries.[37] These observations allude to the importance of minimizing

endothelial injury by improved design of stents and balloons as well as correct deployment technique. Intravascular ultrasound has demonstrated its utility in providing superior technical results that may have a beneficial impact on the incidence of DES LST.[38]

Experimental studies with engineered endothelial cell implants indicate a powerful role for endothelial cells in altering the ECM profile that may minimize neointimal hyperplasia.[39] Seeding endothelial cells on stents prior to implantation may become a viable approach in the future. Pharmacological approaches have centered on increasing the expression of endothelial nitric oxide (NO) synthase (eNOS) and, subsequently, the availability of NO.[40] Nitric oxide participates in the control of vascular healing by attenuating inflammation and inhibiting SMC proliferation and migration. The strategies to increase eNOS are potential therapeutic approaches to treat neointimal hyperplasia. Estradiol has been shown in experiments to promote vascular healing and reduce SMC proliferation.[41] However, a feasibility study involving 30 patients who had stents placed in de novo coronary lesions after the stents were immersed in a solution of estradiol failed to demonstrate any significant reduction in rates of restenosis.[42]

It is well recognized that somatic stem cells in the bone marrow can differentiate into vascular endothelial cells and SMCs. It has been hypothesized that cytokine release after vascular injury induces mobilization, proliferation, and homing of these precursor cells to sites of arterial injury. The bone marrow–derived cells participate in the healing response, as well as lesion formation. Recently, the use of antibodies directed against a specific receptor present on circulating bone marrow progenitor cells has been proposed as a viable treatment strategy for accelerating vascular healing and minimizing subacute stent thrombosis after DES placement. The Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man (HEALING-FIM) study involved implantation of metal stents coated with antibodies against CD34.[43] The technology has created much clinical interest and is presently being evaluated in a small series of patients.

Another approach is to supplement growth factors to accelerate endothelial restitution. Vascular endothelial growth factor (VEGF) is a powerful regulator of endothelial growth and function. Experimental studies have shown both vasculoprotective and potentially atherogenic properties of VEGF. Studies in animal models have shown reduction in neointimal proliferation that may lead to inclusion of VEGF in future restenosis therapies.[44]

Finally, polymeric and metal bioabsorbable stents that "dissolve" slowly after implantation are promising stent technologies that can be loaded with large amounts of drug or multiple agents.[45-47] Bioabsorbable stents fulfill the ideal requirement for endovascular prosthesis by providing initial scaffolding support to prevent vessel recoil and negative remodeling, without the continuous vessel trauma caused by a permanent implant. Ongoing studies are evaluating the safety and efficacy of these newer devices.

Conclusion

The elucidation of the molecular and cellular mechanisms of inflammation and proliferation in vascular injury and repair powered the development of DES technology. Despite the significant benefits of DES compared with BMS in randomized clinical

Main Points

- The relative contributions of individual factors to the development of restenosis appear to differ considerably between drug-eluting stents (DES) and bare-metal stents.
- The major pathologic finding distinguishing thrombosed from patent DES was evidence of greater delay in arterial healing as manifested by persistent fibrin deposition and reduced endothelial coverage.
- In one study, thrombi were more common in stents with incomplete neointimal coverage, and the degree of endothelialization was less complete in DES patients.
- Predictors of DES late stent thrombosis include stenting across ostia of branch points, bifurcations, previous sites of brachytherapy and highly necrotic plaques, as well as proximal or distal plaque disruption with stent implantation.
- Evolving strategies to achieve restoration of normally functioning endothelium following percutaneous coronary intervention revolve around improvements in DES deployment technique, bioabsorbable stents, therapies based on genes and stem cells, pharmacotherapy combinations, and supplementation with growth factors.

trials and registries, significant challenges remain. Newer approaches will shift away from the present day strategy of creating injury and inflammation and then trying to control the consequences of a maladaptive tissue healing response, and will instead focus on restoration of structural and physiological recovery of the vessel to normal function. Combination chemotherapy, bioabsorbable stents, and cell-based therapies are likely to provide effective solutions for the prevention of restenosis and LST in complex lesions and patients. ■

References

1. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420:868-874.
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005; 352:1685-1695.
3. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. *J Am Coll Cardiol*. 1993; 21:15-25.
4. Schwartz RS, Edwards WD, Bailey KR, et al. Differential neointimal response to coronary artery injury in pigs and dogs. Implications for restenosis models. *Arterioscler Thromb*. 1994; 14:395-400.
5. Schwartz RS, Chronos NA, Virmani R. Preclinical restenosis models and drug-eluting stents. *J Am Coll Cardiol*. 2004;44:1373-1385.
6. Taylor AJ, Gorman PD, Kenwood B, et al. Comparison of four stent designs on arterial injury, cellular proliferation, neointima formation, and arterial dimensions in an experimental porcine model. *Catheter Cardiovasc Interv*. 2001; 53:420-425.
7. Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. *Circulation*. 2005;111:2257-2273.
8. Welt FG, Rogers C. Inflammation and restenosis in the stent era. *Arterioscler Thromb Vasc Biol*. 2002;22:1769-1776.
9. Marx SO, Jayaraman T, Go LO, Marks AR. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. *Circ Res*. 1995;76:412-417.
10. Suzuki T, Kopia G, Hayashi S, et al. Stent-based delivery of sirolimus reduces neointimal formation in a porcine coronary model. *Circulation*. 2001;104:1188-1193.
11. Poon M, Marx SO, Gallo R, et al. Rapamycin inhibits vascular smooth muscle cell migration. *J Clin Invest*. 1996;98:2277-2283.
12. Fajadet J, Morice MC, Bode C, et al. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. *Circulation*. 2005;111:1040-1044.
13. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315-1323.
14. Arnal I, Wade RH. How does Taxol stabilize microtubules? *Curr Biol*. 1995;5:900-908.
15. Drachman DE, Edelman ER, Seifert P, et al. Neointimal thickening after stent delivery of paclitaxel: change in composition and arrest of growth over six months. *J Am Coll Cardiol*. 2000;36:2325-2332.
16. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation*. 2003;107:38-42.
17. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004; 350:221-231.
18. Hwang CW, Edelman ER. Arterial ultrastructure influences transport of locally delivered drugs. *Circ Res*. 2002;90:826-832.
19. Levin AD, Vukmirovic N, Hwang CW, Edelman ER. Specific binding to intracellular proteins determines arterial transport properties for rapamycin and paclitaxel. *Proc Natl Acad Sci USA*. 2004;101:9463-9467.
20. Hwang CW, Levin AD, Jonas M, et al. Thrombosis modulates arterial drug distribution for drug-eluting stents. *Circulation*. 2005;111:1619-1626.
21. Kereiakes DJ, Choo JK, Young JJ, Broderick TM. Thrombosis and drug-eluting stents: a critical appraisal. *Rev Cardiovasc Med*. 2004;5:9-15.
22. van Beusekom HM, Whelan DM, Hofma SH, et al. Long-term endothelial dysfunction is more pronounced after stenting than after balloon angioplasty in porcine coronary arteries. *J Am Coll Cardiol*. 1998;32:1109-1117.
23. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans. Delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.
24. Kotani JI, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents. Angioscopic findings. *J Am Coll Cardiol*. 2006;47:2108-2111.
25. Finn AV, Kolodgie FD, Harnek J, et al. Differential response of delayed healing and persistent inflammation at sites of overlapping sirolimus- or paclitaxel-eluting stents. *Circulation*. 2005; 112:270-278.
26. Kereiakes DJ, Wang H, Popma JJ, et al. Periprocedural and late consequences of overlapping Cypher sirolimus-eluting stents: pooled analysis of five clinical trials. *J Am Coll Cardiol*. 2006; 48:21-31.
27. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126-2130.
28. Ong ATL, Hoye A, Aoki J, et al. Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation. *J Am Coll Cardiol*. 2005;45:947-953.
29. Ong ATL, McFadden EP, Regar E, et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol*. 2005; 45:2088-2092.
30. Moreno R, Fernandez C, Hernandez R, et al. Drug-eluting stent thrombosis. Results from a pooled analysis including 10 randomized studies. *J Am Coll Cardiol*. 2005;45:954-959.
31. Bavry AA, Kumbhani DJ, Helton TJ, et al. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med*. 2006;119:1056-1061.
32. Farb A, Burke AP, Kolodgie FD, Virmani R. Pathological mechanisms of fatal late coronary stent thrombosis in humans. *Circulation*. 2003;108:1701-1706.
33. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement. Results from the PREMIER registry. *Circulation*. 2006; 113:2803-2809.
34. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007;297:159-168.
35. Feres F, Costa JR, Abizaid A. Very late thrombosis after drug-eluting stents. *Catheter Cardiovasc Interv*. 2006;68:83-88.
36. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents. A review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol*. 2006;47:175-181.
37. Rogers C, Parikh S, Siefert P, Edelman ER. Endogenous cell seeding. Remnant endothelium after stenting enhances vascular repair. *Circulation*. 1996;94:2909-2914.
38. Mintz GS, Weissman NJ. Intravascular ultrasound in the drug-eluting stent era. *J Am Coll Cardiol*. 2006;48:421-429.
39. Nugent HM, Edelman ER. Tissue engineering therapy for cardiovascular disease. *Circ Res*. 2003;92:1068-1078.
40. von der Leyen H, Gibbons G, Morishita R, et al. Gene therapy inhibiting neointimal vascular lesion: in vivo transfer of endothelial cell nitric oxide synthase gene. *Proc Natl Acad Sci USA*. 1995;92:1137-1141.
41. New G, Moses J, Roubin G, et al. Estrogen-eluting, phosphorylcholine-coated stent implantation is associated with reduced neointimal formation but no delay in vascular repair in a porcine coronary model. *Catheter Cardiovasc Interv*. 2002;57:266-271.
42. Abizaid A, Albertal M, Costa MA, et al. First human experience with the 17-beta-estradiol-eluting stent: the Estrogen and Stents to Eliminate Restenosis (EASTER) trial. *J Am Coll Cardiol*. 2004;43:1118-1121.
43. Aoki J, Serruys PW, van Beusekom HM, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) registry. *J Am Coll Cardiol*. 2005;45:1574-1579.
44. Walter DH, Cejna M, Diaz-Sandoval L, et al. Local gene transfer of phVEGF-2 plasmid by gene-eluting stents: an alternative strategy for inhibition of restenosis. *Circulation*. 2004;110: 36-45.
45. Vogt F, Stein A, Rettemeier G, et al. Long-term assessment of a novel biodegradable paclitaxel-eluting coronary polylactide stent. *Eur Heart J*. 2004;25:1330-1340.
46. Tamai H, Igaki K, Kyo E, et al. Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. *Circulation*. 2000;102:399-404.
47. Heublein B, Rohde R, Kaese V, et al. Biocorrosion of magnesium alloys: a new principle in cardiovascular implant technology? *Heart*. 2003;89:651-656.