EDITORIAL COMMENT

Drug-Eluting Stents and Late Adverse Clinical Outcomes

Lessons Learned, Lessons Awaited*

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Endothelial cells form a continuous syncytium that separates the intravascular and extravascular space. The endothelium is a selectively permeable and metabolically active vascular component that regulates important pathophysiological processes such as hemostasis, thrombosis, and synthesis of growth factors, nitric oxide, and matrix proteins. Endothelial dysfunction is one of the earliest events in atherogenesis and is often mediated by endothelial cell injury induced by a variety of cardiovascular risk factors. Disruption and damage of the endothelium, such as that which occurs during percutaneous coronary intervention, ultimately results in a predictable regeneration of the endothelium. However, if the injury is excessive, prolonged, or of a nature that limits normal healing, as is clearly documented with brachytherapy, late clinical events will occur, albeit with low incidence but increasing frequency, even with dual antiplatelet therapy.

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In this issue of the *Journal*, Kotani et al. (1) provide sobering angioscopic data on the rate of neointimal coverage of drug-eluting stents (DES) that complement recent pathological and clinical data on the underlying potential mechanisms of late stent thrombosis (LST). They evaluated 25 patients (37 stents, 15 DES, 22 bare-metal stents [BMS]) with angioscopy at 3 to 6 months after stent implantation. Using a subjective grading system based on the neointimal coverage of stent struts, they noted that all 22 BMS (100%) had complete neointimal coverage, whereas in stark contrast only 13.3% (2 of 15) DES had complete coverage. Thrombus, which was not visible angiographically, tended to be more common in DES and in stents without neointimal coverage. This study is limited by small sample size, different BMS, lack of use of paclitaxel-eluting stents, and a relatively short follow-up period. Nonetheless, the study provides mechanistic underpinnings through which DES and/or their individual components may result in LST, defined as >30 days after stent implan-

tation, by suggesting that lack of or delayed neointimal coverage may be an etiologic factor.

ENDOTHELIAL REGENERATION AND VESSEL WALL RESPONSES AFTER STENT IMPLANTATION

The regeneration of iatrogenically denuded endothelium was appreciated as early as the 1950s in distal aortas of rabbits and baboons (2). In these studies it was noted that the endothelium regenerated via mitosis from the margins of the denuded area, from the margins of small vascular channels within the denuded area, and from vasa vasorum. Speculation had even persisted that circulating blood cells were deposited into the denuded area and contributed to the endothelium, an observation now confirmed as the presence of circulating endothelial progenitor cells. Subsequently it was shown that endothelial regeneration is initiated by loss of contact inhibition of adjacent endothelial cells. The extent of de-endothelialization and the speed of regeneration is likely to have direct clinical relevance in mediating adverse clinical sequelae.

Immediately after percutaneous coronary intervention in humans, there is complete destruction of endothelial cells at the injured site. In addition, stent struts penetrate the lipid core in the majority of cases and there is frequent medial damage, conditions that are strongly associated with enhanced inflammation and a propensity toward exaggerated neointima formation (3). The endothelium generally regenerates within one to three months, providing a new barrier to the inherently thrombogenic exposed plaque or stent struts. Pathological studies of human BMS have shown that the early healing phase (<3 days) after percutaneous coronary intervention is manifested by acute deposition of fibrin, platelets, and acute inflammatory cells such as neutrophils, creating in effect a thin, membranous thrombus that is ultimately resorbed (4,5). By two weeks, a matrix-poor neointima is formed, albeit with incomplete coverage of the stent. By one month, enhanced extracellular matrix, along with increasing numbers of smooth muscle cells and fewer chronic inflammatory cells, adds to the volume of neointima, generally completely covering the stent struts. Over six months, proteoglycans and matrix proteins and other products of smooth muscle cells contribute to neointima formation, the extent of which is mediated by many clinical, angiographic, and intrinsic stent factors. These findings are generally reflected in the animal models commonly used to assess safety and efficacy of stents, such as the normal pig coronary artery and hypercholesterolemic rabbit iliac artery models, which show patterns of healing similar to those of humans but with a significantly faster time frame than in human arteries (6).

DES AND THROMBOGENICITY

Both CYPHER (Cordis, Miami Lakes, Florida) (71 to 314 μg slow release sirolimus depending on stent size, 80%

released within 30 days) and TAXUS (Boston Scientific, Natick, Massachusetts) (50 to 209 μg slow-release paclitaxel depending on stent size, data obtained from each respective package insert) stents have closed cell designs and different cell geometry and strut thickness. They both contain cell-cycle inhibitors with different mechanisms of action and different *nonerodable* polymers (67%/33% polyethylene-co-vinyl acetate/poly n-butyl methacrylate for sirolimus and poly(styrene-b-isobutylene-b-styrene) for paclitaxel). Therefore, clinical sequelae may arise from the stent material (316L stainless steel in both stents composed of iron, nickel, and chromium), the respective drugs, or the polymers, which will persist indefinitely in the vessel wall.

Not surprisingly, both the animal data and the few human pathological studies available on DES show fundamental differences in healing compared with BMS. For example, animals treated with BMS uniformly show complete endothelialization by 28 days, whereas animals treated with DES uniformly show a dose-dependent delay in healing, manifested by persistence of fibrin around stent struts, delayed endothelialization, and the presence of inflammatory cells (7–9). This lack of healing persists and may even be accentuated at longer time points, such as 180 days, a time point not routinely studied or previously required in studies with BMS before human clinical trials. Interestingly, animal models seem to reflect safety more specifically rather than efficacy of various stent designs, and a catch-up phenomenon in neointima formation over three to six months has been noted with sirolimus, paclitaxel, and tacrolimus, so that no significant differences in efficacy are seen between BMS and DES (7–9). These findings have led some investigators to suggest that DES efficacy in humans may ultimately be short-lived, but that four to five years of clinical follow-up may be required for certainty because of the temporal differences in efficacy in animal models versus humans (10). Interestingly, despite these concerns, there is a significant discrepancy in efficacy parameters between animal data and clinical results.

However, the more serious concern is not necessarily the potential for late catch-up phenomena, which would generally present as late restenosis and repeat target lesion revascularization, but late stent thrombosis, which would present as sudden death or large myocardial infarction.

HYPERSENSITIVITY REACTIONS AND DES

Virmani et al. (11) initially documented a localized hypersensitivity reaction in a 58-year-old man who died 18 months after CYPHER stent implantation, consisting of fragments of polymer, T-cells, and eosinophils. They implicated the nonerodable polymer, because sirolimus is no longer present in the vessel wall after 60 days and because it has inherent anti-inflammatory properties that would suppress accumulation of such inflammatory cells. Additional data for both systemic (rash, itching, fever, arthralgia, and so on) and localized (eosinophilic peri-stent infiltrates) hyper-

sensitivity reactions were shown by the Research on Adverse Drug Events and Reports (RADAR) project, which concluded that 17 definite or highly likely hypersensitivity cases occurred out of 262 reports potentially associated with DES (12). Four of these 17 cases were accompanied by autopsy data confirming the presence of peri-stent eosinophilic infiltrates. Interestingly, in autopsy series of BMS, no local hypersensitivity reactions were noted in over 400 cases (13). However, in-stent restenosis has been associated with allergies to nickel (stent component) and molybdenum (stent impurity) (14).

LESSONS LEARNED FROM FAILED CLINICAL TRIALS OF DES

It is now clear that both the type of drug and the dose are critically important in determining efficacy and adverse events (15). For example, in the Actinomycin-eluting stent Improves Outcomes by reducing Neointima hyperplasia (ACTION) trial, a first-look subset analysis of 39 of 240 patients showed a significantly higher rate of target lesion revascularization (TLR) with actinomycin-D compared with a comparable BMS (16), necessitating early termination of the trial. The rationale for any potential clinical usefulness of this stent-drug combination was based on 28-day animal data, which apparently had shown both safety and efficacy. However, as the investigators note in the discussion of that study, unpublished animal data after the trial was initiated showed that the polymer was safe at 180 days but that all doses of actinomycin-D resulted in medial thinning, necrosis, fibrin deposition, and inflammation, all signposts of poor vessel healing (16). Similarly, the Study to Compare Restenosis Rates between Quest and QuaDDS-QP2 (SCORE) showed that 7-hexanoyltaxol, a paclitaxel derivative loaded on four to six acrylate polymer sleeves (each 2.4-mm sleeve is loaded with 800-μg 7-hexanoyltaxol, totaling over 4,000 μg drug per stent, compared with ~110 μg paclitaxel on the TAXUS stent), was associated with increased stent thrombosis (3.2% vs. 0% at 1 month, 7.1% vs. 0.7% at 6 months, and 10.3% vs. 0.7% at 12 months) and death/myocardial infarction rates (11.9% vs. 2.1% at 1 month, 15.9% vs. 2.1% at 6 months, and 19.0% vs. 2.1% at 12 months) (17). Unpublished data from porcine models purportedly obtained after SCORE enrollment showed intense inflammation, granulomas, fibrosis with severe narrowing, and occlusion in vessels stented with the QuaDDS stent or polymer-only sleeves (17). Pathological specimens from atherectomy specimens derived from in-stent restenosis patients in this trial showed persistent fibrin, extensive proteoglycan matrix, and incomplete healing (18).

The underlying reasons for this haste to bring DES to clinical trials can be debated and may be obvious to many. Additionally, the previously accepted standard for BMS safety was the 28-day stent animal models. Unfortunately, the potential for long-term adverse sequelae in these studies was not anticipated by regulatory bodies, sponsors, or

investigators. The investigators and sponsors are to be commended for detecting these problems early, stopping the trials, and publishing these results, which hopefully will lead to improved scientific validation of preclinical data before clinical trials. One of the key lessons of these DES experimental studies, aside from the uncertainty of translating efficacy animal data to humans, a lesson clearly learned from the failure of multiple agents to prevent restenosis in humans, is that safety animal data at 28 days does not necessarily predict long-term results and that longer time points in animals are needed before approval of such devices for clinical trials.

CLINICAL TRIALS AND LATE ADVERSE EVENTS

Clinical efficacy. Contrary to that in animal models and the brachytherapy experience in humans, the current clinical data, although limited, do not suggest a catch-up phenomenon. For example, in the First-in-Man study, serial quantitative intravascular ultrasounds obtained up to four years in 23 event-free patients treated with CYPHER stents showed no significant further increase in neointima formation between two and four years (19). Similarly, there is a durable efficacy in the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de novo Native Coronary Artery Lesions (RAVEL) with three-year follow-up (20), and two-year follow-up in Sirolimus-Eluting Stent in de Novo Native Coronary Lesions (SIRIUS) study (21) and the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry (22). Meta-analyses of the randomized clinical trials also have not shown an increased risk of adverse events related to DES (23,24).

Adverse events. However, case reports and observational studies are increasingly reporting a definite increase, albeit small, in the incidence of LST, particularly during clopidogrel withdrawal (25–27). For example, McFadden et al. (26) reported four cases of LST approximately one year after DES placement, all associated with antiplatelet therapy withdrawal. Ong et al. (27) reported an incidence of LST of 0.35% superimposed on an incidence of 1.0% in the first 30 days. In the largest observational study that clearly reflects real-world findings in which off-label use was common in more difficult lesions and in higher-risk patients, Iakovou et al. (25) reported a 30-day incidence of 0.6% and an LST incidence of 0.7%. In these observational studies, one can assume that these are the minimum rates, because it is likely that some cases are missed because of a lack of follow-up or because of clinically silent stent thromboses. A uniformly independent predictor of LST is antiplatelet therapy withdrawal, either clopidogrel or both aspirin and clopidogrel, as well as diabetes, increased stent length, bifurcation lesions, and crush stenting, in which the overall stent thrombosis rate approaches 5% (28).

Further confirmation of the specific role of DES versus BMS in stent thrombosis was recently provided by Rodriguez

et al. (29) from the Argentine Randomized Trial of Coronary Stents versus Bypass Surgery (ERACI III). They showed a 3.1% (7 of 225) incidence of stent thrombosis during 18.3 ± 8.8 months of follow-up with four cases after 30 days of stent implantation. Consistent with previous reports, six of seven cases (86%) were associated with discontinuation of clopidogrel. Both CYPHER and TAXUS stents had a similar incidence of stent thrombosis (1.9% vs. 1.5%, respectively). Of significant interest, of the four patients that had multistent placement and concomitant DES and BMS in different arteries, all of the stent thromboses occurred at DES sites, strongly implicating stent-specific etiologies in LST. These data are further supported by the fact that DES are associated with paradoxical vasoconstriction at the proximal and distal edges of stents ~6 months after implantation, whereas BMS are not associated with this phenomenon (30). Late stent thrombosis in BMS also occurs and is likely underappreciated, although it does not seem to have a similar incidence, particularly because many of the DES stent thromboses occur during clopidogrel withdrawal. Farb et al. (4) reported that LST in BMS, aside from the obvious exposure to brachytherapy, is also associated with stenting across the ostia of major arterial branches; plaque disruption in the non-stented arterial segment within 2 mm of the stent margin; stenting of markedly necrotic, lipid-rich plaques with extensive plaque prolapse; and in diffuse in-stent restenosis.

Clinical implications. As with all things that seem too good to be true, there is a bit of forced reality emerging regarding the clinical usefulness of DES. Long-term follow-up of randomized clinical trials and registries continues to show a relative benefit of DES over BMS and no overall higher risk of major myocardial infarction or death. However, most of this benefit is attributable to reduced TLR, an end point that is accentuated in favor of DES by the oculostenotic reflex that invariably is associated with mandatory angiographic follow-up. Although the morbidity of increased TLR affects patients in a tangible way and is clearly reflected by their desire to avoid repeat procedures, selected patients, such as those who cannot tolerate or have a real possibility of needing to be withdrawn from clopidogrel, and their physicians, may be trading a mean 10% to 15% absolute benefit in reduced TLR for a mean 0.5% to 2% absolute risk of LST, with LST being a much higher morbid event often associated with death and major myocardial infarction. Of course, in those who are withdrawn from clopidogrel, the risk is much higher but difficult to quantitate, because reports of large numbers of patients with clopidogrel withdrawal and the associated risk of LST have not been reported.

Therefore, a reassessment of the universal use of DES, at least in their current formulations, may be on the horizon and should lead to a scholarly debate regarding the optimal indications of DES. Clearly, in patients at risk for aspirin/clopidogrel withdrawal, such as patients who generally do not tolerate many medications, those who may require elective surgery, and those with a history of bleeding disorders, such as prior gastrointestinal bleeding, one would have to weigh the

risks and benefits carefully before using a DES. For example, in a nondiabetic patient with a discrete lesion in a large vessel, one may predict a very small absolute benefit of using a DES. Because it is generally difficult to predict when patients may require aspirin or clopidogrel withdrawal, this strategy may become more common if the issue of LST persists.

As occurs with many new clinical advances, the initial exuberance generally gives way to the realities presented by real-world findings, particularly as indications expand beyond the package insert and a reassessment occurs regarding the optimal indications. As we move beyond the euphoria of curing restenosis, we now must address the issues of targeted use of DES; optimal duration of antiplatelet therapies and novel stent/polymer designs, such as erodable, noninflammatory polymers or no polymers whatsoever (31); enhancement of endothelial cell coverage (32); reduction of peri-stent inflammation; and hypersensitivity stimuli. Although the goal of curing restenosis is close at hand, we now must strive to bring long-term safety and efficacy to new frontiers. The interventional community and our patients should expect nothing less than continued success in our unparalleled achievements in treating cardiovascular disease.

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