Drug-Eluting Stents: Role of Stent Design, Delivery Vehicle, and Drug Selection

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Increasing focus has recently been directed toward the different parameters of drug-eluting stents—stent design, delivery-vehicle materials, and drug properties—and the manner in which each of these elements may affect the function of the stents. Several specific characteristics of design may affect restenosis, although design optimization often presents a choice between acute procedural success and long-term biological stability. The influence of design parameters such as strut thickness and cell configuration is described. Polymer material has frequently been used to coat drug-eluting stents, although some agents, such as paclitaxel, can be attached directly to the stent's surface, obviating the need for a polymer layer. The properties of agents used in drug-eluting stents and how those properties affect delivery and long-term outcome are discussed, as is the influence of the disease state of the target vessel on stent safety and efficacy.
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Early pilot studies reviewed elsewhere in this journal indicated overwhelmingly positive results with stent-based drug delivery for the prevention of restenosis.[1,2] Early clinical trials of most agents appeared promising. However, larger studies with longer-term follow-up have recently led to the conclusion that efficacy and safety may differ among agents and among stents. Consequently, increased focus has been directed toward the different parameters of drug-eluting stents, including the stent backbone, materials used as drug-eluting vehicles, and the physicochemical properties of the agents themselves.

Current and future generations of drug-eluting stents will require optimization of each of these parameters in order to provide greatest efficacy and safety. This article will review how these specific elements—stent design, delivery-vehicle materials, and drug properties—may affect the functioning of drug-eluting stents.

Stent Design

In an era of near-universal stent use in coronary interventions, metal-stent design has become refined to a point where nearly all vessels, regardless of diameter, length, and location, are able to receive stents with high procedural success and low complication rates. Developments in strut configuration, strut thickness, and delivery-balloon technology have resulted in important procedural attributes, including reduced device profiles, increased flexibility and conformability, and fluoroscopic visibility. The same refinements that have led metal-stent design to this level have also limited restenosis, with rates from recent clinical studies in the 10%–20% range. Recent clinical studies suggesting an impact of metal-stent design on coronary restenosis[3,4] have a foundation in several animal studies that established a link between design (and depth of injury) and subsequent neointimal thickening or experimental restenosis.[5,6]

Several specific design parameters may affect restenosis, although design optimization often presents a choice between acute functionality and long-term biological stability. For example, stents with thinner struts may have less visibility but also have more favorable flow dynamics within the lumen, providing less turbulent flow and less corresponding platelet activation and inflammatory cell recruitment. Novel designs using metals other than steel will allow thinner struts with retained radio-opacity.

Current metal stents can be categorized into "closed-cell" and "open-cell" configurations. Closed-cell stents have cells whose bounded area does not change as the stent is flexed (a diamond shape is an example of a closed cell), while open-cell stents have cells that grow in area as the stent is flexed (a coil spring is an example). Stents with an "open-cell" configuration tend to have greater conformability to curved segments after expansion, but therefore have greater variations in arterial surface coverage between the inner and outer curvatures of a tortuous segment than do stents with a "closed-cell" design. Similarly, stents with greater surface coverage offer greater luminal circularity, minimizing tissue growth as the vessel remodels to regain optimal flow characteristics,[7] but at the same time have the potential to be rigid and nonconformable and to afford limited access to side branches.

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Overall, in the current era, competing aspects of stent design allow practitioners to choose stents specific to the needs and challenges of a given lesion. That is, in a straight, large vessel without involved side branches, a fairly rigid but high-surface-coverage stent can be used, whereas in a smaller vessel with tortuosity or side-branch involvement, a more flexible stent with larger openings between struts may be the better option, albeit at the expense of lower surface coverage and perhaps slightly higher restenosis rates. Already, creative, novel designs are under development that will accommodate the widely varied requirements of coronary anatomy, permitting optimized coverage and shape without compromise of flexibility during delivery or conformability after expansion.

Combining current, highly refined metallic-stent designs with polymer materials (discussed below) has been the standard approach in several drug-eluting stent initiatives. As current-generation metallic stents with or without polymer coatings are used for drug delivery, a new series of questions arises regarding the impact of stent design on stent performance and how clinicians will choose among drug-eluting stents in the future. No longer will acute deliverability and procedural success be the only goals of stent design. In particular, recent experimental data suggest that stent configuration directly determines the pattern and degree of drug delivery achieved by the stent. Hwang et al reported that even at steady state conditions, sodium fluorescein delivered from a stent surface was detectable in blood vessels in a pattern directly representative of the stent-strut configuration.[8] In other words, following delivery of even highly soluble and rapidly diffusing drugs, homogenous drug delivery throughout the vessel and into all areas and depths of the vessel wall is not achieved. From the perspective of stent design, this finding implies that designs that maintain regular strut spacing despite expansion in various anatomical circumstances (tortuous segments, bifurcations, ostial locations, etc)

will provide the most regular and predictable drug delivery. For drugs with wide toxic-to-therapeutic ratios, it may be that regularity of strut spacing is less important and that adequate doses can be applied to the stent's surface so that, despite broad variability in the location of delivery, adequate doses are achieved. On the other hand, drugs with narrower toxic-to-therapeutic ratios may suffer from inadequate dosing at sites where stent struts lie far apart, and possibly supratherapeutic or toxic dosing at sites where stent struts bunch together due to vessel curvature or asymmetric expansion.

A final aspect of stent design that may have unique effects on drug delivery is stent–vessel wall apposition. Clearly, in order for a stent to deliver its payload of drug into the target vessel, it needs to be apposed directly to the vessel wall. In the absence of such apposition, drug released from the surface is released into the bloodstream and drawn into the systemic circulation rather than deposited into the underlying vessel. The possibility exists that a handful of novel stent designs, constructed to allow greater flexibility and deliverability, may suffer from poor stent–vessel wall apposition, particularly in tortuous vessel segments. Bench-top modeling must be coupled with animal and then clinical confirmation of applicability before firm clinical recommendations can be made for choices among drug-eluting stents.

Stent Coatings

The results of years of careful preclinical histologic and biochemical analysis defining the cellular and molecular events that follow stent implantation have recently been borne out in several clinical reports. The sequence of events that commences with platelet and leukocyte deposition at sites of stent implantation, followed in turn by smooth-muscle-cell proliferation, migration, and production of extra cellular matrix, culminates in the final product of neointimal thickening, a rind of tissue growing within the bounds of a metallic stent.[9–21]

Each of these elements in the vascular response to stenting can be affected by alterations in the stent's surface. Surface polish and texture,[22] as well as added layers of different metals such as gold, can alter platelet and plasma protein deposition and cell adhesion.[23,24] Polymer material has frequently been added to the surface of metallic drug-eluting stents so that the polymer may serve as a drug reservoir, eluting the drug slowly over time. Numerous polymer materials drawn from a variety of biomaterials have been studied experimentally as stent coatings. These materials have included bioerodible polymers such as poly-L lactic acid and biostable polymers such as polyurethane derivatives and silicone-based polymers, among others.[25–27] Despite promising initial testing suggesting biocompatibility, many polymer materials have been associated with marked inflammation when used as coatings on implanted stents.

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Recently, however, long-term animal studies have identified a variety of polymers from diverse families that appear inert and biocompatible. This progress has allowed all of the major device developers to enter the field of drug-eluting stents with polymers that are safe from a vascular, biological perspective. It is worth noting, as described elsewhere in this journal, that there are pharmacologic agents that can be attached directly to a stent's metal surface, thereby obviating the need for a polymer layer. One such agent is paclitaxel, which by virtue of its long tissue retention after delivery, remains in the vessel for long periods, even after only short-term, in effect, bolus, delivery.[28] Use of an agent that does not need a polymer layer simplifies device manufacturing and testing, which may enhance reliability and safety.

Drug Selection

Detailed understanding of the biological events that follow stent implantation has led to a selection of agents for drug-eluting stents that target specific elements of this biological process. Furthermore, agents have been selected based on physicochemical properties that optimize deposition and retention in the vessel wall following delivery. The agents to be discussed in other articles in this supplement exhibit broad biological actions. Even agents with purported specific antiproliferative properties, such as paclitaxel and sirolimus, in actuality have far broader actions. Both sirolimus and paclitaxel possess potent immunoregulatory and anti-inflammatory function and affect cell migration and motility. Mechanisms of efficacy and toxicity, therefore, likely derive from the combination of these effects, rather than solely from antiproliferative properties. In this complex biological milieu, differentiating agents simply on the basis of antiproliferative mechanisms, for example, or compartmentalizing

them into classes such as cytotoxic or cytostatic, only captures a very small part of the story. Such efforts to categorize agents vastly understate the breadth of their biological actions.

Just as the agents being developed for delivery from stents have beneficial effects on diverse aspects of vascular healing, they also can have adverse effects on the vessel wall. For example, agents such as sirolimus and paclitaxel, which impair proliferation of vascular smooth-muscle cells, also inhibit proliferation of endothelial cells. Of note, higher concentrations of paclitaxel are required to affect endothelial cells than to affect smooth-muscle cells in vitro,[29] although this distinction has not been clearly defined in vivo. Slowing or preventing endothelial-cell regrowth may in turn prolong the danger period for stent thrombosis, as has been reported with vascular brachytherapy.[30] Furthermore, once the drug has been exhausted from the stent and vessel wall, if the surface remains incompletely covered with endothelium, late adverse responses such as platelet deposition, plasma protein adsorption, and eventual tissue growth may occur. The net effect could then be late "catch up," in which tissue growth and restenosis are delayed but not completely prevented.

The final differentiating features among agents are physicochemical properties such as partitioning coefficients, diffusivity, and solubility, as well as presence or absence of protein binding. All are increasingly recognized as important considerations in agent selection. Hwang et al used mathematical modeling techniques to predict the degree and location of drug delivery on the basis of some of these physicochemical parameters.[8] Their work revealed that hydrophobic drugs diffused poorly following delivery, thereby allowing higher doses to be maintained in blood vessels. Paclitaxel, for example, is highly hydrophobic and would therefore be predicted to have prolonged residence time in blood vessels following stent-based delivery. In other words, delivery for a short period of time may result in retention for long periods of time in the vessel wall. This phenomenon would be seen particularly in atherosclerotic settings with large lipid components within the arterial structure. A corollary, then, would be that one could deliver paclitaxel for a brief period of time without requiring a polymer membrane. Despite the fact that the stent's payload is delivered in its entirety only in the first few days or weeks following stenting, one would predict that the drug would be deposited in the vessel wall and remain there perhaps for weeks or months. This attribute of paclitaxel is not generalizable, and drugs that are more water soluble or have greater diffusivity might well require prolonged delivery in order to achieve prolonged vessel wall exposure.

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Vascular Disease State

The final parameter that bears consideration in complete evaluation of drug-eluting stents is the disease state of the target vessel. Virtually all preclinical development takes place either in tissue culture or in the normal arteries of experimental animals. As reviewed in other articles in this journal, experimental models primarily include porcine coronary and rabbit iliac arteries, among others. In such vessels, free of atherosclerotic burden, the target reservoir for drug therapy is quite different from that encountered in clinical settings. In clinical use, drug-eluting stents are placed in noncircular, eccentrically diseased, atherosclerotic sites with highly variable composition and mechanical properties. Furthermore, comorbid illnesses such as diabetes or hypertension may have discrete biological effects on the atherosclerotic plaque and on the response to stent-based drug delivery. These parameters prove extremely difficult to model in any predictive fashion in preclinical trials.

Hence, the burden falls on clinical trials to identify safety and efficacy in various disease states. The difference between animals and humans in the time course of biological events that follow stenting presents a particular challenge to stent development. The biological cascade described earlier in this article, although qualitatively nearly identical between animal models and humans, occurs over a much more

protracted period of time in clinical settings. Therefore, drug-eluting efforts perfected to treat only experimental animals may fail in clinical settings by virtue of inadequate duration of delivery.

Two other clinical settings deserve particular mention. The first is in-stent restenosis. Once established, in-stent restenosis has been difficult to treat with long-term success, with the only proven, effective therapy being vascular brachytherapy. In fact, many patients with in-stent restenosis eventually require coronary bypass surgery as the final therapeutic intervention. Small pilot studies have been undertaken to investigate treatment of established in-stent restenosis with a drug-eluting stent placed within the previously deployed stent. Some preliminary reports have suggested poor efficacy and poor safety in this setting, while other reports have shown promise. The response of in-stent–restenosis neointimal thickening to mechanical intervention has not been well defined and the cellular events that ensue may well be quite different qualitatively and quantitatively from those that follow initial stenting of *de novo* atherosclerotic plaque. For this reason, the target tissue may not respond to current generations of drug-eluting stents or may be subject to toxicities not seen in primary atherosclerotic-plaque stenting. While the notion of using drug-eluting stents to treat in-stent restenosis is inherently appealing, careful clinical scrutiny is warranted before any such practice is adopted. Proof of efficacy of drug-eluting stents in primary atherosclerotic plaques with low rates of in-stent restenosis does not guarantee either safety or efficacy in the setting of in-stent restenosis.

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The other atherosclerotic disease state that has been targeted in pilot studies with drug-eluting stents is peripheral vascular disease. In particular, proposals have been developed and pilot studies initiated to test drug-eluting stents in sites of high restenosis risk, such as the superficial femoral artery in arterial disease below the knee. While the biological events that follow stenting in these locations are probably quite close to those that follow coronary stenting of *de novo* atherosclerotic plaques, the unique requirements of stent design and alterations in vessel size seen in these peripheral arterial disease settings may impose novel and stringent requirements on a drug-eluting stent. Specifically, it may be necessary to develop self-expanding stents or stents capable of expansion to larger sizes in order to treat vascular disease at such sites, and the dose of drug required to treat larger, thicker, more highly elastic vessels may be substantially higher than that required in coronary interventions. As with in-stent

Main Points

- Stent design, delivery-vehicle materials, and drug properties all affect the functioning of drug-eluting stents.
- Several specific design parameters may affect restenosis, although design optimization often presents a choice between acute functionality and long-term biological stability.
- Recent experimental data suggest that stent-strut configuration directly determines the pattern and degree of drug delivery achieved by the stent. In addition, stents that allow greater flexibility may suffer from poor stent–vessel wall apposition, resulting in less drug released directly into the target vessel.
- Polymer material has frequently been used to coat drug-eluting stents, although some agents, such as paclitaxel, can be attached directly to the stent's surface, obviating the need for a polymer layer.
- Agents used in drug-eluting stents exhibit broad biological actions. For example, mechanisms of efficacy and toxicity for sirolimus and paclitaxel likely derive from a combination of immunoregulatory and anti-inflammatory function and effect on cell migration and motility, rather than solely from antiproliferative properties.

restenosis, specifically designed trials addressing the hypothesis of efficacy in peripheral arterial disease settings are required before any claims of safety or efficacy in these locations can be made.

Conclusion

The current generation of drug-eluting stents builds upon decades of research in metal-stent design and evaluation of polymer material. In ensuing generations, stent designs will likely be engineered for optimal drug delivery to specific lesions while maintaining the refinements already achieved for acute procedural success. Furthermore, it is likely that novel polymer materials and pharmacologic agents will be engineered or chosen for biological activity against specific elements of the broad cascade of events that follow vascular stenting. As this evolution takes place, it is likely that the promising, but imperfect, drug-eluting stents developed to date will show improved performance, safety, and predictability. ■

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