Optimal Stent Design for Drug Delivery

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The efficacy and safety of drug-eluting coronary stents might differ depending on the pharmacologic agents and stent delivery systems used. Recent research has focused on the various constituents of drug-delivery stents, including the stent backbone, materials used as drug-delivery vehicles, and the physicochemical properties of the pharmacotherapeutic agents themselves. Metal stents coated with an outer layer of polymer (bioabsorbable or non-bioabsorbable) can be drug-loaded, thus providing more controlled and sustained drug delivery and allowing more optimal drug–tissue interactions. Among the next generation of drug-eluting stents will be a stent that uses the non-bioabsorbable polymer phosphorylcholine to release the sirolimus analogue ABT-578; another stent will use a highly deliverable cobalt-chromium metal alloy stent platform and, for the first time, a bioabsorbable polymeric coating (thin-film polylactic acid) for drug encapsulation and release.

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Although early studies indicated overwhelmingly positive results with stent-based drug delivery for the prevention of restenosis,[1,2] and early clinical trials of several agents seemed promising, larger studies with longer-term follow-up have subsequently led to the conclusion that efficacy and safety might differ among pharmacologic agents and among stent delivery systems. Consequently, focus has been directed toward the various constituents of drug-delivery stents, which include the stent backbone, materials used as

drug-delivery vehicles, and the physicochemical properties of the pharmacotherapeutic agents themselves. Future generations of drug-delivery stents will require optimization of each of these parameters to provide the greatest efficacy and safety. This article will review how each of these specific elements—stent design, delivery-vehicle materials, and drug properties—might affect the "net" function of drug-delivery stents.

Table 1
Specific Considerations Regarding Polymer-Based Elution in Drug-Eluting Stents

- Noninflammatory and nonthrombogenic
- Predictable drug elution kinetics (timing and dose)
- Elastomeric without surface integrity changes (eg, cracking, peeling)
- No alteration of incorporated drug activity
- No alteration of the structural and operational stent characteristics
- Logistic factors: sterilization, stability, shelf-life, and expense

Mechanisms of Stent-Based Drug Delivery

After vascular injury in animal models, the cellular and subcellular mediators of restenosis are found within the arterial wall within hours and persist for days to weeks.[3-9] Hence, stents that deliver drugs might be an ideal platform, because they are deployed against the vessel wall and provide prolonged tissue contact. Stent-based drug delivery has been accomplished by three distinct mechanisms. First, bioabsorbable polymeric stents can be loaded with a drug that is eluted slowly over time. Second, metal stents can have a drug bound to their surface or embedded within macroscopic fenestrations or microscopic nanopores, thus providing more rapid drug delivery. Finally, metal stents coated with an outer layer of polymer (bioabsorbable or non-bioabsorbable) can be drug-loaded, thus providing more controlled and sustained drug delivery, which might allow more optimal drug–tissue interactions.

Most purely polymeric bioabsorbable stents reported in the literature have induced severe inflammation. An exception to this early experience is the poly-L-lactic acid (PLLA) Igaki-Tamai stent.[10] Metal stents coated with an outer layer of either non-bioabsorbable or bioabsorbable polymers, such as PLLA, and biostable polymers, such as polyurethane derivatives and silicone-based polymers, among others[11–13] might allow an optimal combination of conventional stent performance and scaffolding, as well as controlled and sustained drug release.

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The current first-generation devices use this approach. To be successful, the polymer itself must be biologically inert. Interestingly, polymers that are inert by routine biomaterial testing methods might prove to be markedly proinflammatory when applied to a stent and implanted intravascularly. In addition, polymer coatings must be nonthrombogenic and must tolerate the many mechanical forces that are characteristic of stent deployment, including plastic deformation and manipulation. Thus, several specific considerations for polymer-based drug delivery exist (Table 1).

There are pharmacologic agents that can be attached directly to a stent's metal surface, thereby obviating the need for an additional polymer layer. Use of an agent that does not require a polymer layer for delivery would simplify device manufacturing and testing, which might in turn enhance reliability and safety. One such agent is paclitaxel, which by virtue of its long tissue retention after delivery remains in the vessel wall for protracted periods, even after brief or "bolus" exposure/delivery.[14,15] However, although nonpolymeric delivery of paclitaxel was promising in early pilot trials, it was not particularly effective in a large-scale, multicenter, pivotal randomized trial. At late angiographic (8 month) and clinical (9 month) follow-up of patients treated with either the nonpolymeric, paclitaxel-eluting stent or the bare metal, MULTI-LINK PENTA® stent (Guidant Corp., Indianapolis, IN), in-stent late lumen loss was decreased (0.81 mm vs 0.98 mm, respectively; $P = .003$), whereas in-stent binary restenosis (14.9% vs 20.6%, respectively; $P = .076$) and target vessel failure (11.9% vs 14.5%, respectively; $P = .12$) were not significantly reduced.[16]

In both preclinical and clinical experience, there has been a great deal of interest in the development of a polymer coating that might effect sustained drug delivery from a

stent yet remain biologically inert itself.[17-19] In a porcine model, fibrin-coated, heparin-loaded tantalum stents reduced the incidence of thrombosis, inflammation, and death when compared with stents coated with polyurethane.[20] Phosphorylcholine and other inert polymeric coatings have recently been accepted in clinical practice, with reputed benefits of reducing thrombus deposition and no deleterious effect on late vessel healing. The BiodivYsio Stent in Randomized Control Trial (DISTINCT) compared the BiodivYsio phosphorylcholine-coated stent with the ACS Duet™ (uncoated) stent (Guidant Corp.) in a randomized fashion. Although the study was not adequately powered to determine a difference in thrombotic events, no thromboses were observed to 30 days in the phosphorylcholine-coated group, and two thrombotic complications occurred in the uncoated stent group. At 6-month follow-up, however, no significant differences in late lumen loss or binary restenosis (approximately 20%) were observed between the two treatment groups.

In preclinical trials, covalently bound heparin was found to reduce thrombosis but had no effect on restenosis in stented porcine coronary arteries.[21,22] In the BENESTENT-II clinical pilot trial, heparin-coated stents seemed to reduce the need for systemic anticoagulation, as well as bleeding events and length of hospital stay, when compared with the results observed with non–heparin-coated stents in BENESTENT-I.[23] The Heparin-Coated Stents in Small Coronary Arteries (COAST) trial, which evaluated small-vessel (2.0–2.6 mm) revascularization with the JoFlex stent (either heparin-coated or uncoated) versus balloon angioplasty alone, found no significant differences in angiographic restenosis or event-free survival between any of the three treatment groups.[24] The HOPE trial was designed to determine whether heparin coating of a stent could reduce the need for postimplantation oral thienopyridine therapy. Subacute thrombotic complications were observed in two patients who received heparin-coated stents without post-stent thienopyridine therapy. The weight of clinical information currently available does not suggest a reduction in either angiographic restenosis or clinical ischemic events after use of heparin-coated versus uncoated stents.

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An additional challenge for the development of locally delivered therapies is the determination and titration of local drug concentration in the targeted tissues. In preclinical studies, tracer compounds are often used as surrogates to model the delivery of drug from a particular platform. Modeling is complex, however, because the pharmacokinetics of drug delivery might vary dramatically, depending on the physicochemical properties of the drug, influence of the stent/platform design, as well as the disease state of the target vessel. Drugs that are hydrophilic might diffuse rapidly through tissues and "wash out" before a biologic effect can be registered. Conversely, those that are hydrophobic might have long-term residence in target tissues but might distribute asymmetrically or inhomogeneously. Differences in stent design might affect the distance between stent struts after deployment and thus the points of distribution of drug into the target tissue. Furthermore, the nature of the disease state in the vessel wall (ie, whether it is a de novo atherosclerotic lesion, fibromuscular postangioplasty restenosis, in-stent restenosis, or a lesion in a saphenous vein graft) might dramatically impact the pharmacokinetics of drug delivery from stent to target tissue. There are several specific pharmacologic considerations for drugs to be used in targeted, stent-based delivery systems (Table 2). Although a specific targeted

Table 2
Specific Pharmacologic Considerations Regarding Drug-Eluting Stents

- Targeted mechanism(s) of action
- Understanding precise pharmacokinetics and pharmacodynamics (radial/axial distribution)
- Clarify therapeutic–toxic window (optimal dosimetry)
- Custom dosimetry under varying anatomic/patient conditions
- Multidrug possibilities
- Systemic and especially local toxicity—vascular compatibility at prescribed dose and kinetics
- Logistic factors: effects of sterilization, stability over time, and expense

Table 3
Drug-Eluting Stents: Pharmacologic Reduction of Restenosis

Anti-inflammatory Immunomodulators	Antiproliferative	Migration Inhibitors, ECM-Modulators	Promote Healing and Re-endothelialization
Dexamethasone	QP-2, Taxol	Batimastat	BCP671
M-prednisolone	Actinomycin	Prolyl hydroxylase inhibitors	VEGF
Interferon γ-1b	Methotrexate	Halofuginone	Estradiols
Leflunomide	Angiopeptin	C-proteinase inhibitors	NO donors
Sirolimus (and analogues)	Vincristine	Probucol	EPC antibodies
Tacrolimus	Mitomycin		Biorest
Mycophenolic acid	Statins		Advanced coatings
Mizoribine	C-MYC antisense		
Statins	Sirolimus (and analogues)		
Cyclosporine	RestenASE		
Tranilast	2-chloro-deoxyadenosine		
Biorest	PCNA ribozyme		

ECM, extracellular matrix; PCNA, proliferating cell nuclear antigen; VEGF, vascular endothelial growth factor; NO, nitric oxide; EPC, endothelial progenitor cell.

mechanism of action is an important consideration, many agents have been demonstrated to have multiple mechanisms by which they might suppress the restenotic process (Table 3).

Implications of Stent Design

The evolution of bare metal stents in areas of strut configuration, strut thickness, and delivery-balloon technology has resulted in refined procedural attributes, including reduced profiles, increased flexibility and conformability, and enhanced fluoroscopic visibility. Refinements in metal-stent design have also limited restenosis, with rates from recent clinical studies in the 10% to 12% range.[25-28] Novel designs currently under development will accommodate the widely variable requirements of coronary anatomy and permit improved endoluminal coverage without compromise of flexibility during delivery or conformability after expansion.

Optimized drug-delivery stents require a marriage between refined metal stent designs and drug-delivery technology. Highly deliverable metal stent platforms with thin struts and conformable configurations might have to be modified to accommodate polymeric coating and to allow adequate and homogeneous drug delivery. 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-delivery stents in the future. No longer will procedural deliverability and procedural success be the only goals of stent design. In particular, recent experimental data suggest that stent-strut configuration directly determines the pattern and degree of drug delivery achieved by the stent. Hwang and colleagues[29] 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. In other words, after deployment of even highly soluble and rapidly diffusing drugs, homogenous drug delivery throughout the vessel with uniform concentration at various depths of the vessel wall is not achieved. From the perspective of stent design, this observation suggests that designs that maintain regular strut spacing despite expansion in various anatomical circumstances (eg, tortuous segments, bifurcations, ostial locations) will provide the most regular and predictable drug delivery. For drugs with wide toxic-to-therapeutic ratios, such as members of the sirolimus family, it might 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

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other hand, drugs with narrower toxic-to-therapeutic ratios, such as paclitaxel, might suffer from inadequate dosing at sites where stent struts lie far apart and possibly from supratherapeutic or toxic dosing at sites where stent struts bunch together owing to vessel curvature or asymmetric expansion.

Current and Future Drug-Eluting Stent Systems

In the United States, the two drug-eluting stent systems currently approved by the U.S. Food and Drug Administration are the CYPHER™ (sirolimus-eluting) stent from Cordis/Johnson and Johnson (Miami Lakes, FL) and the TAXUS™ (paclitaxel-eluting) stent from Boston Scientific (Natick, MA). The design features of these two stent platforms are relatively similar: both are closed-cell-design stents with inert and non-erodible polymeric coatings. However, the differences between the drugs used in these two devices are much greater. Sirolimus, along with its analogues everolimus and ABT-578, was developed primarily as a means of suppressing transplant rejection, whereas paclitaxel is a widely used cancer chemotherapeutic agent. Animal studies have suggested that the window between efficacy and toxicity for paclitaxel may be narrower than for sirolimus or its analogues. The differences in configuration between the CYPHER™ stent and the TAXUS™ stent do confer slightly enhanced procedural deliverability to the latter, although this difference pales in comparison with the anticipated differences between these first-generation devices and second-generation drug-eluting stents currently under evaluation. The ongoing REALITY trial in Europe is a randomized comparison of the TAXUS™ and CYPHER™ stents and will allow further insights into the relative safety and efficacy of these two devices.

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Among the next generation of drug-eluting stents will be the Endeavor™ stent (Medtronic, Inc., Minneapolis, MN), which uses the non-erodible polymer phosphorylcholine to release the sirolimus analogue ABT-578. This will be among the first drug-eluting stents to use a non–stainless steel alloy as the foundation for a polymer-coated, drug-eluting stent. There is little doubt that the thin-strut, cobalt-chromium alloy stent itself (Driver) will have enhanced deliverability and side-branch access compared with either the TAXUS™ or CYPHER™ stents, although comparable antirestenotic efficacy remains to be determined. The ENDEAVOR III trial, currently under way, is a randomized comparison of the CYPHER™ and Endeavor™ stents with late angiographic follow-up, which should define the relative antirestenotic efficacy of the two devices.

An even more novel approach is found with Guidant Corporation's CHAMPION™ stent, described elsewhere in this supplement. In brief, the CHAMPION™ stent uses a highly deliverable metallic stent platform and, for the first time, a bioabsorbable polymeric coating (thin-film polylactic acid) for drug encapsula-

Main Points

- Stent design, delivery-vehicle materials, and drug properties all affect the functioning of drug-delivery stents.
- Drug-eluting stents provide an ideal platform to prevent stenosis because they are deployed against the vessel wall and have prolonged tissue contact.
- Several specific design parameters might 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 might suffer from poor stent–vessel wall apposition, resulting in less drug being 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.
- Among the promising stent-based drug delivery devices currently being studied, the CHAMPION™ stent is unique in its use of a metallic platform coated with a fully bioabsorbable polymer for drug encapsulation and release.

tion and release. The potential benefits of this absorbable polymer are its restriction to the abluminal (outer) surface of each strut (so that drug and polymer are not exposed to flowing blood in the arterial lumen) and the eventual degradation of the polymer to carbon dioxide and water, which are free of any toxic byproducts. Thus, the stent design "guarantees" that there will be complete elimination of the drug from the stent over a finite period of time without drug retention, which could pose a threat for late adverse events months to years after implantation.

The CHAMPION™ stent will be studied clinically in the FUTURE IV trial, projected to begin patient enrollment in the summer of 2004. This trial will randomize nearly 1000 patients to either the CHAMPION™ stent or an approved drug-eluting stent (either TAXUS™ or CYPHER™ will be chosen as the control stent for the study). The primary endpoint for the study will be an angiographic measure of restenosis 8 months after stenting (in-segment late lumen loss). Additional secondary endpoints will include additional intravascular ultrasound and angiographic measures of restenosis, as well as clinical findings such as major adverse cardiac events and clinical restenosis (eg, target vessel revascularization, target vessel failure). However, the use of a primary endpoint that is a surrogate for clinical restenosis, a feature shared by both the FUTURE IV and ENDEAVOR III trials, with a noninferiority equivalency trial design, is novel and confers much greater statistical power in relatively small numbers of patients.

Interestingly, the high frequency of follow-up angiography planned for this trial (> 80% of patients) might well drive clinical restenosis rates upward. This will happen as a function of the protocol-mandated angiographic re-look in asymptomatic patients, which can uncover a clinically silent stenosis, which the operator then proceeds to treat. Hence, in interpreting the clinical results of these two trials, it will be important to consider the target vessel revascularization rates relative to one another, not relative to other reported rates in the literature from prior studies that might have used less comprehensive strategies for angiographic follow-up.

Conclusion

Future generations of stents will likely be engineered for optimal drug delivery to specific lesions while continuing to refine the bare metal stent platform to enhance acute procedural success. Furthermore, it is likely that novel polymer materials and pharmacologic agents will be chosen for biological activity in specific disease states or vascular beds. ■

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