Drug-Eluting Stents: Clinical Perspectives on Drug and Design Differences

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Although the introduction of coronary stents has significantly improved the treatment of patients with coronary artery disease, restenosis, due to neointimal proliferation following stent deployment and associated with a return of ischemic symptoms, has remained a critical concern. Recent studies have shown that the use of drug-eluting stents to deliver antiproliferative agents directly to the vessel wall dramatically reduces the rate of restenosis. However, important differences exist among stent designs, drug-delivery vehicles, and choices of pharmacologic agents that can significantly affect the safety and efficacy of each device. Although engineers, vascular biologists, and clinicians all agree that clinical success of drug-eluting stents requires careful integration of the individual system components, the optimal combination remains to be determined.
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Key words: Sirolimus • Paclitaxel • Stent design • Bifurcation lesions

Although the introduction of coronary stents has significantly improved the treatment of patients with coronary artery disease, coronary artery restenosis due to neointimal proliferation and associated with return of symptoms as well as major adverse coronary events (MACE) within months after intervention, have remained of significant concern. Recent studies show that the use of drug-eluting coronary stents to deliver antiproliferative agents directly to the vessel wall can dramatically reduce the rate of restenosis.[1-6] However, the efficacy and safety of various drug-eluting stents may differ

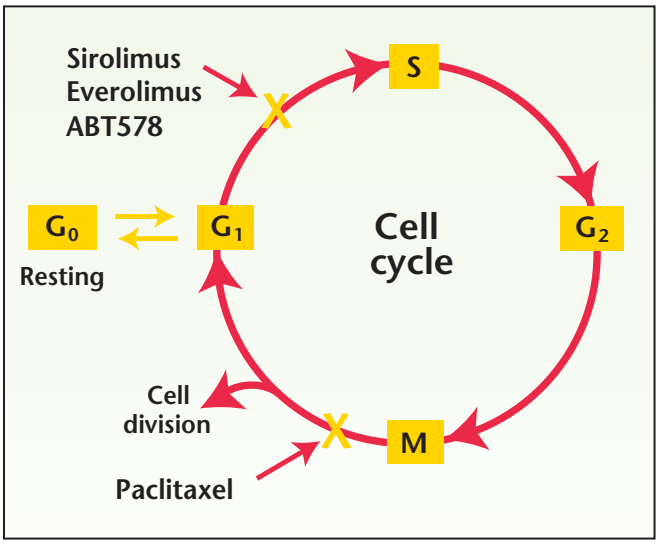

Figure 1. *The cell cycle consists of 5 basic steps: mitosis (M), gap phase 1 (G1), dormancy (G0), synthesis (S) and premitosis or gap phase 2 (G2). Sirolimus and its analogs, everolimus and ABT578, interfere early in the cell cycle, inhibiting the passage of cells from G1 to S phase. Paclitaxel's primary site of action is to halt the cell cycle during the M phase.*

depending on the delivery system and pharmacologic agent used.[7] The clinical success of drug-eluting stents requires the meticulous integration of the individual system components: stent design, drug-carrier vehicle, and pharmacologic agent.[3]

This article describes the pathophysiology of restenosis and the rationale for the use of immunosuppressants and antiproliferative agents. It discusses individual system components and also examines the relationships among stent design, drug carrier, and pharmacologic agent and how these relationships may affect issues confronted in real-world, interventional settings.

Pathophysiology of Restenosis

The pathophysiology of restenosis involves a complex cascade of events that begins in the early minutes and hours after the vascular injury caused by stenting. Focal fibrin deposition with thrombus formation is usually observed within the first 3 days after stent implantation and is proportional to the depth of injury to the artery wall by the stent struts.[8] Platelets and macrophages produce growth factors that induce an inflammatory reaction at the injury site, which leads to smooth muscle cell migration and proliferation over the following days to weeks.[8] Extracellular matrix production then adds bulk to this neointimal thickening, or hyperplasia, which is the key mechanism responsible for in-stent restenosis and the central target of the antiproliferative effects of current drug-eluting stents.[9]

Rationale for Drug-Eluting Stents

A rational therapeutic approach to preventing restenosis is the use of drugs that interfere with the biological processes involved in the development of neointimal hyperplasia. Local drug delivery via the stent results in minimal systemic exposure and decreased risk of toxic drug effects. The antiproliferative and immunosuppressive agents used in currently available stent systems, as well as those in clinical development as described below, exert their pharmacologic actions in specific phases of the cell cycle (Figure 1). The cell cycle consists of 5 basic steps: dormancy (G0), gap phase 1 (G1), synthesis (S), gap phase 2 (G2), and mitosis (M). After mitosis, cells enter a gap period (G1) during which the cells begin to produce the proteins and enzymes necessary for DNA synthesis. Late in the G1 phase, cells approach the restriction point in which they can either become quiescent (the G0 phase) or remain metabolically active (the S phase). DNA synthesis occurs during the S phase. The cell progresses into G2 and prepares for mitosis by manufacturing RNA and mitotic spindles. The cell cycle then repeats, starting with mitosis.[8,9]

Immunosuppressive Agents

Sirolimus (rapamycin) and its analogs, everolimus and ABT578, are immunosuppressants with both anti-inflammatory and antiproliferative properties that interfere early in the cell cycle, inhibiting the passage of cells from G1 to S phase (Figure 1). Drugs that inhibit the cell cycle in the G1 phase are considered cytostatic and may be less toxic than drugs that act later in the cell cycle.[8]

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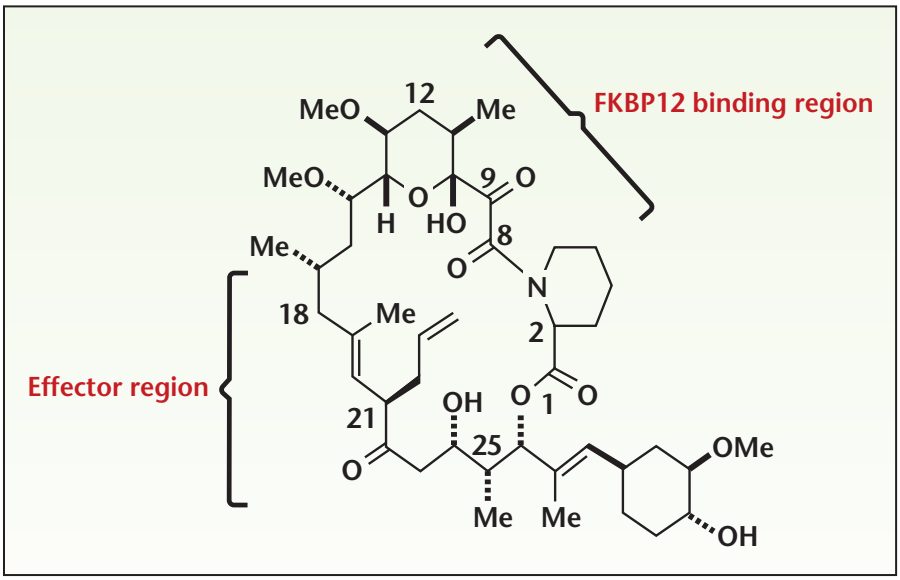


Figure 2. *Chemical structure of sirolimus.*

coronary artery restenosis (Figure 2).[10] Sirolimus binds to FKBP12, forming a complex that then binds and inhibits the mammalian target of rapamycin (mTOR). Binding of mTOR inhibits the downregulation p27, thereby increasing intracellular levels of this factor, which is responsible for inhibiting cyclin-dependent kinase (CDK)-clin complexes.[9] The result is the arrest of the G1-S phase of the cell cycle and, ultimately, of T-cell, B-cell, and smooth muscle cell proliferation.[11] Because such cell cycle inhibition by sirolimus is considered cytostatic rather than cytotoxic, smooth muscle cells treated with sirolimus maintain their viability.[11]

Everolimus

Everolimus, an active immunosuppressant and antiproliferative compound, and a rapamycin analog, has shown promise in preventing heart and kidney transplant rejection. Like sirolimus, it binds to FKBP12 and blocks mTOR. It has also been shown to reduce smooth muscle cell proliferation in human transplant allografts.[12] Everolimus has increased solubility in organic solvents compared with sirolimus and has shown similar ability to inhibit smooth muscle cell proliferation despite a 2- to 3-fold lower affinity for FKBP12. Slightly more lipophilic than sirolimus, everolimus may be more rapidly absorbed into the arterial wall where it is stored in fatty tissue and plaque, close to the injury site.[12]

ABT578

ABT578, a new synthetic analog of rapamycin, is a potent antiproliferative and anti-inflammatory agent with a broad therapeutic window. ABT578 was initially evaluated as a treatment for rheumatoid arthritis.[13] Similar to sirolimus and everolimus, ABT 578 inhibits mTOR. In vitro studies demonstrating ABT578 inhibition of human coronary artery, smooth muscle cell proliferation led to the development of the Endeavor™ ABT578-eluting stent (Medtronic AVE, Santa Rosa, CA) discussed below.[13]

Antineoplastic Agents: Paclitaxel

Antineoplastic agents also show promise for preventing restenosis as a component of drug-eluting stents.[4-6] Paclitaxel is the most widely investigated agent in this group of drugs (Figure 3). Paclitaxel was and continues to be a widely used cancer chemotherapeutic agent. The cytotoxic activity of paclitaxel was identified in 1971 from an extract of the bark and, eventually, the needles of the Pacific yew tree, *Taxus brevifolia*. Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization.[4,14] This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis (Figure 4).[14] As a result, the cell cycle is halted during the M phase. In addition, paclitaxel may inhibit angiogenesis and promote cell death.[9] Paclitaxel has been shown to inhibit smooth muscle cell proliferation in a dose-dependent manner and to prevent neointimal formation after stenting in animal models.[4,15,16]

Stent Coating

Current first-generation drug-eluting coronary stents accomplish drug delivery via polymer coating, and the stent coating is an essential part of drug-eluting stent function. Importantly, cardiovascular system implants may be more demanding in terms of both safety and efficacy than those in other parts of the body, as polymers proven safe and biocompatible in other milieus can provoke intense inflammation in the setting of vascular stenting.[17] Even subtle changes in the stent strut itself or in its material or coating may be proinflammatory, especially at sites of deep vascular injury. To be successful, a

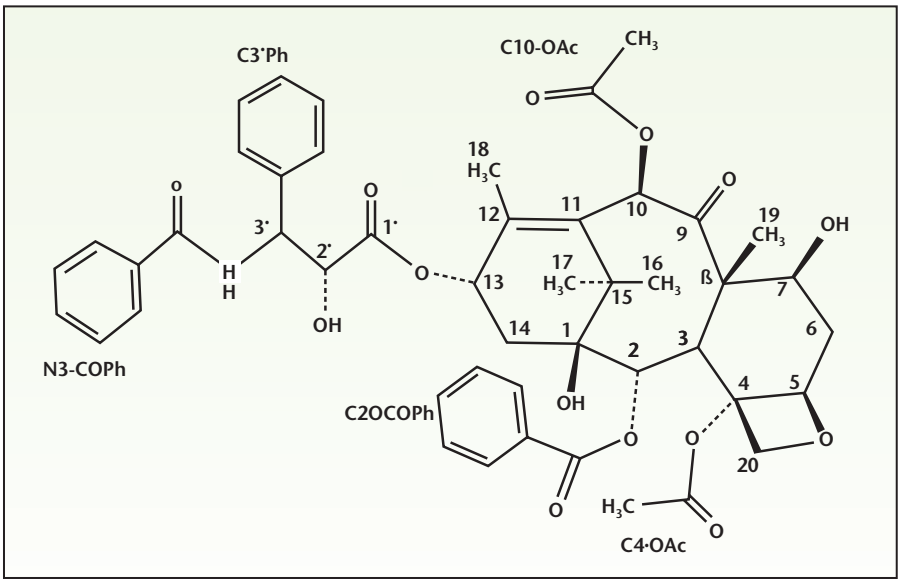


Figure 3. *Chemical structure of paclitaxel.*

polymer used in drug-eluting cardiac stents must satisfy several specific criteria. It must be biologically inert, nonthrombogenic, and noninflammatory; able to tolerate the dynamic forces characteristic of stent deployment in the coronary circulation such as plastic deformation and manipulation; allow predictable drug elution kinetics; maintain surface integrity (eg, no cracking or peeling); and not alter the structural and operational characteristics of the stent.[7]

Drug-Polymer Assembly Strategies

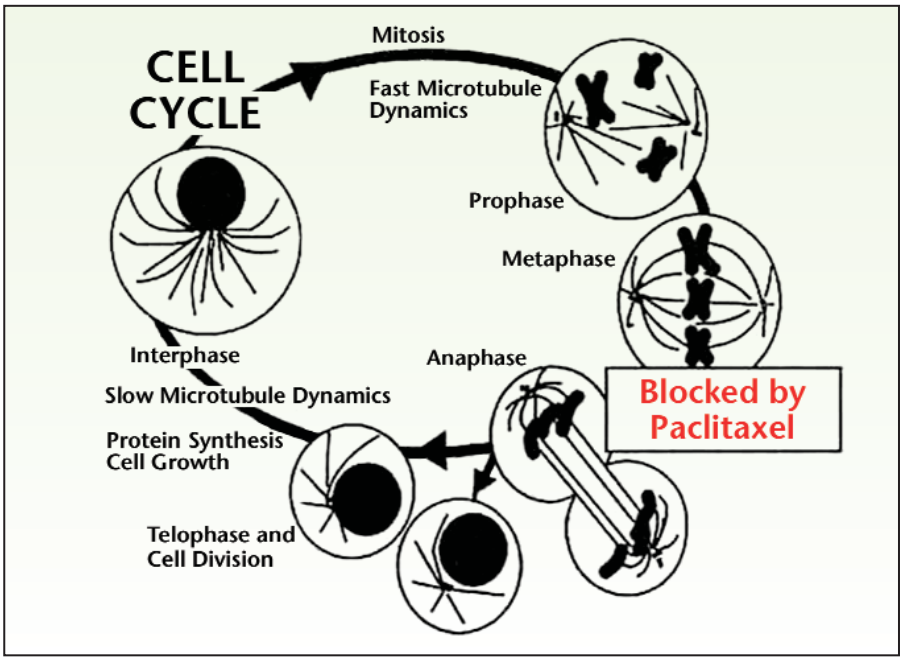
Stent-based drug delivery can be accomplished via several different drug/polymer assembly strategies that encourage an even and continuous release of drug.[9]

- The matrix strategy combines copolymers and antiproliferative agent into 1 phase. The mixture is applied uniformly onto the stent and drug release depends on drug diffusion through this inoculated polymer layer.[9]
- The reservoir technique places antiproliferative drug directly onto the stent. Polymers are then added to the stent, encasing the antiproliferative agent inside the polymer phase. Drug becomes accessible to the surrounding tissue after diffusing across the polymer.[9]
- A third assembly technique combines the matrix and reservoir strategies. This approach involves applying a mixture consisting of a polymer and the antiproliferative agent, which is then coated with a drug-free polymer topcoat. The drug diffusion rate through each of the phases determines drug release.[9] There is some evidence, from early work done by Cordis Cardiology with sirolimus, that the addition of a topcoat to a durable drug-loaded polymer can greatly delay drug delivery.
- A final drug-eluting design option avoids the use of a polymer. In this case, the antiproliferative drug is bound to the surface of the stent or embedded within the macroscopic fenestrations. Turbulent blood flow or chemical decay promotes the release of drugs from these stents.[7,9]

Impact of Stent Design

The final component of the drug-eluting stent system is the design of the bare metal stent that underlies

Figure 4. *As illustrated, paclitaxel alters microtubule dynamics involved in cell division. It binds to microtubules; stabilizes microtubule structure; forms bundles and multiple asters; inhibits cell division, motility, shape change; and alters inflammatory cell function.*[14]



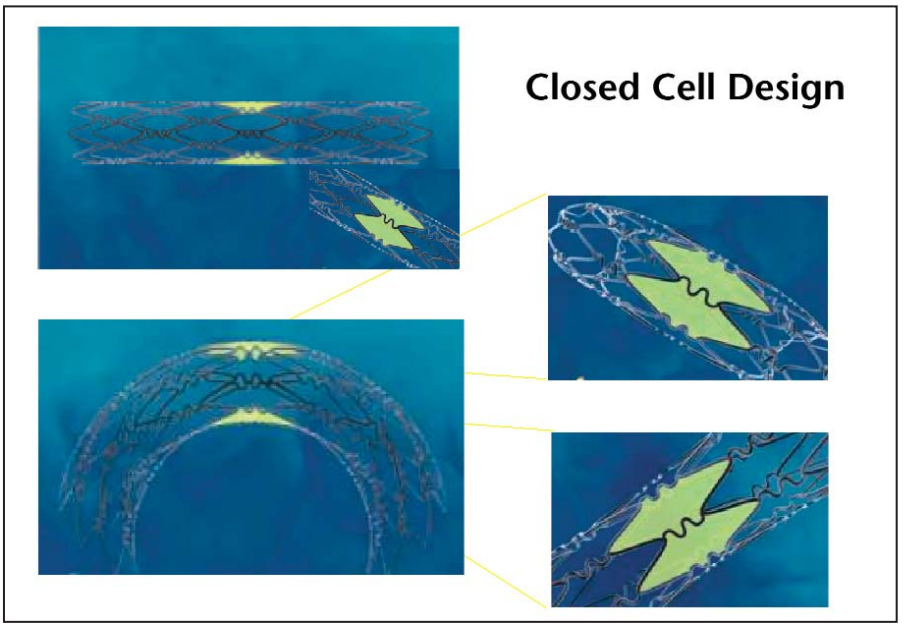


Figure 5. *Closed cell design stents retain the same area within any given stent cell, regardless of how stretched or compressed the stent becomes. Closed cell designs are expected to deliver drug evenly to all aspects of the artery.*

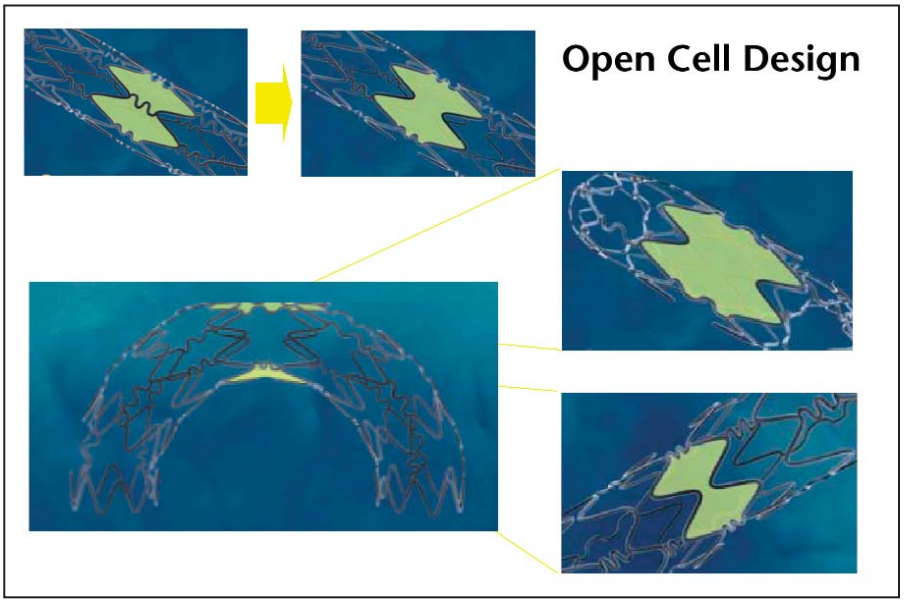
the drug delivery device. Researchers have speculated that the architecture of the stent itself may influence the degree of injury and the rate of restenosis. Thus, variables such as strut thickness, pattern, and composition may influence the success of a given stent.[9,18-21]

Stents have been categorized into what have been termed closed-cell and open-cell designs. Closed-cell design stents retain the same area within any given stent cell, regardless of how stretched or compressed the stent becomes in settings of curvature or eccentric lesion (Figure 5). From the perspective of drug delivery, closed cell designs should, theoretically, deliver drug evenly to all aspects of the artery.

Alternatively, open cell design stents are those in which the area enclosed by a single strut can vary greatly, meaning that the area to be dosed with drug from the surrounding stents may be quite small on the inner aspect of a curve, and much larger on the outer aspect of the curve (Figure 6). Thus, the same polymer/drug coating applied to a stent with an open cell design might potentially achieve inadequate dosing on the outer curvature, where the struts are widely spaced, and toxic dosing on the inner curvature, where the struts are closer together.

Hwang and colleagues recently evaluated the impact of cell design and drug properties on drug delivery.[22] The results of their investigations challenged the prevailing view that drug-eluting stents delivered drug and bathed the artery homogeneously, allowing complete drug delivery and saturation of the entire vessel wall. In a series of studies, the investigators coated bare-metal stents of various shapes and sizes with sodium fluorescein and implanted them in excised bovine arteries to determine whether the stent design itself dictated where and for how long the drug resided. They found that even at steady-state conditions, sodium fluorescein delivered from the surface of the stent was visible in blood vessels in a pattern that directly represented the stent-strut pattern (Figure 7).[22] Thus, after deployment

Figure 6. *In open cell design stents, the area enclosed by a single strut can vary greatly, and the area dosed with drug from the surrounding stents can be either quite small on the inner aspect of the curve, or much larger on the outer aspects of the curve. As a result, a polymer drug coating applied to a stent with an open cell design may achieve inadequate dosing on the outer curvature and potentially toxic dosing on the inner curvature, where the struts are closer together.*



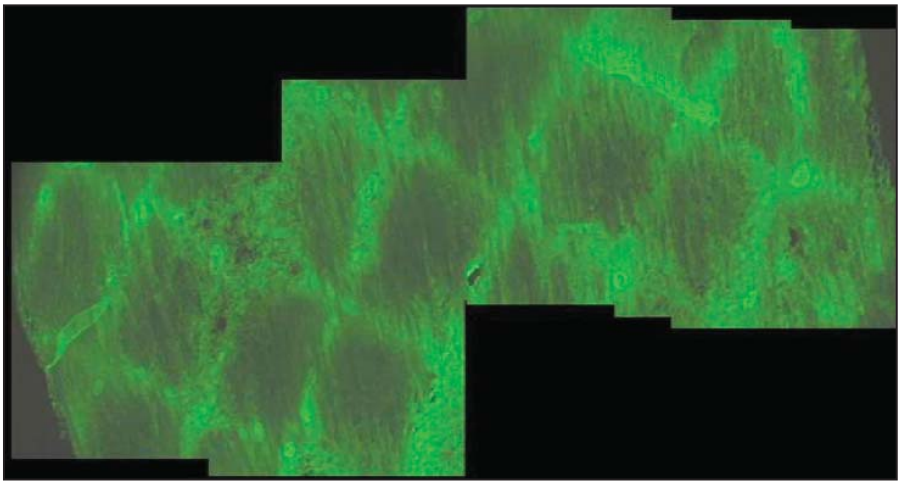


Figure 7. *Image of fluorescein distribution at 200 µm from luminal surface of bovine carotid artery. Reprinted with permission from Hwang et al.*[22]

of even highly soluble and rapidly defusing drugs, homogeneous drug delivery throughout the vessel with uniform concentration at various depths of the vessel wall was not achieved.[7] The authors note, however, that the distribution of hydrophobic compounds, such as paclitaxel, was slightly less dependent on strut configurations than that of hydrophilic compounds.[22] From the perspective of stent design, these findings suggest that optimal drug delivery requires symmetric expansion of stents with homogeneous distribution of struts.[22] Other investigators suggest that for drugs with wide toxic-to-therapeutic ratios, such as sirolimus, the regularity of strut spacing may be less important, because adequate doses may be achieved despite broad variability in the location of delivery. Conversely, drugs with narrower toxic-to-therapeutic ratios, perhaps including paclitaxel, may suffer from suboptimal dosing at sites where stent struts bunch together due to asymmetric expansion or vessel curvature.[7]

Current Drug-Eluting Stent Systems

The 2 currently approved drug-eluting stent systems in the United States are the CYPHER® sirolimus-eluting stent (Cordis Cardiology, Miami Lakes, FL) and the TAXUS™ (paclitaxel-eluting) stent (Boston Scientific, Natick, MA). Both systems use a closed-cell design with inert and nonerodible polymeric coatings.[2,6] Everolimus- and ABT578-eluting stent systems are also in clinical trials.[12,13] All are described briefly below.

The CYPHER Stent

The CYPHER sirolimus-eluting stent is a metal stent coated with a mixture of sirolimus (140 mg/cm^2) blended with synthetic polymers and then covered with a second coating of drug-free polymer that acts as a diffusion barrier. After stent implantation, sirolimus is slowly released from the polymer over a period of about 30 days.[11] Clinical trials with sirolimus-eluting stents have demonstrated reduced incidence of clinical and angiographic restenosis as well as MACE.[1,2,23] In recent follow-up studies, persistent inhibition of neointimal hyperplasia has also been demonstrated for up to 2 years after sirolimus-eluting stent implantation.[24]

The TAXUS Stent

Some early studies with different formulations of paclitaxel-eluting stents demonstrated a lack of sustained effects and some vascular toxicity.[15,25] However, recent investigations with the polymer-based paclitaxel-eluting TAXUS stent have produced more promising results with regard to safety and efficacy.[5,6] As compared with bare-metal stents, a low dose (1 µg/mm^2), slow-release, polymer-based paclitaxel-eluting stent markedly reduced the rate of restenosis at 9 months.[6] This efficacy was maintained at 1 year follow-up with no apparent safety concerns.[26] Several studies comparing the CYPHER and TAXUS stent systems in "workhorse" lesions, as well as several specific lesion and clinical subsets, are underway. Preliminary results regarding bifurcation stenting are discussed below.

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The Endeavor™ ABT578-Eluting Stent

The Endeavor ABT578-eluting stent (Medtronic, Inc., Minneapolis, MN) uses phosphorylcholine coating as a drug carrier on the Driver stent.[13] This stent has thinner struts made possible by the use of a stronger cobalt-chromium alloy resulting in a lower profile and potentially improved deliverability.[13] The ENDEAVOR III trial, a randomized comparison of the CYPHER and

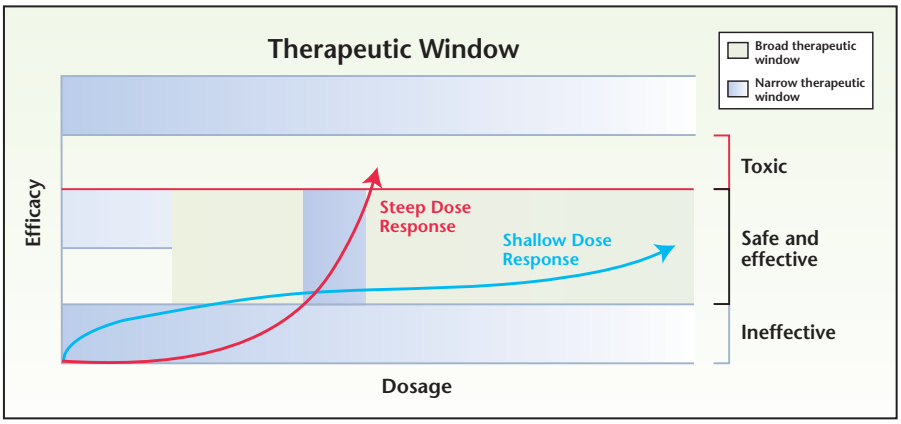


Figure 8. *Therapeutic window for drug delivery. Note that Drug A (blue arrow) has a fairly shallow dose response, whereby it can surpass the efficacy threshold, but not reach the toxic threshold. In contrast, Drug B (red arrow) has a much steeper relationship and could cross from efficacy into toxicity over a fairly narrow range.*

Endeavor stents with late angiographic follow-up, recently completed enrollment and is currently in followup.

Everolimus-Eluting Stents

The Challenge™ everolimus-eluting stent (Biosensors International Inc., Singapore) is a stainless steel stent covered by a bioabsorbable composite coating that contains everolimus (97 µg everolimus/mm^2) within a biodegradable polyhydroxy acid matrix.[12,27] Initial clinical experience (FUTURE I and II trials) found the everolimus-eluting stent to be safe and effective in reducing neointimal hyperplasia and restenosis.[12] The Xience™ everolimus-eluting stent (Guidant Inc., Indianapolis, IN) also releases a similar dose of everolimus, but uses a non-erodible polymer and the cobalt-chromium Vision™ stent. Initial data from the SPIRIT FIRST trial[28] suggested high safety and efficacy, and larger randomized studies are scheduled to begin early in 2005.

Clinical Concerns

In spite of the demonstrated success of cardiac stent-based drug delivery, many concerns regarding efficacy and safety remain unresolved. Two specific areas of concern are the safety of overlapping stents and the challenges posed by bifurcation stenting.

Overlapping Stents

Concerns regarding overlapping stents relate, in part, to the potential for drug-eluting stents to deliver toxic levels of drug in the areas of stent overlap. Clearly, the magnitude of risk very much depends on the toxic-to-therapeutic ratio of the drug eluted from the stent. As can be seen in Figure 8, Drug A has a fairly shallow dose response, whereby it can surpass the efficacy threshold, but then not reach the toxic threshold until great dose escalation. In contrast, Drug B has a much steeper relationship and could cross from efficacy into toxicity over a fairly narrow range. Thus, if one considers the area of stent overlap as a zone where additional doses may be delivered, drugs that have steeper toxic-to-therapeutic ratios have less safety in this setting.

Investigators conducting the recent TAXUS VI trials looked at patients who received overlapping stents. The study compares TAXUS Moderate-Release paclitaxel (N = 63) with controls (N = 61). Although the investigators found no significant difference between the 2 groups, a trend toward more frequent early MACE was seen in patients receiving the overlapping TAXUS Moderate-Release stents compared with controls (1.6 vs 7.9%, P = 0.21). Paclitaxel has a relatively narrow toxic-to-therapeutic ratio.[29]

Bifurcation Stenting

An additional concern is whether currently available drug-eluting stents will produce satisfactory results in "real world" interventional practice settings, where more complicated patients and lesions (bifurcated, ostial, etc.) are common. In response to concerns about wider applicability of drug-eluting stents, Serruys and colleagues compared sirolimus- and paclitaxel-eluting stents in a consecutive series of patients with de novo lesions treated with drug-eluting stent implantation in both main vessel and side branch.[30] During 1 phase of practice, all procedures were initially done with sirolimus-eluting CYPHER stents, and then a wholesale switch was made to TAXUS paclitaxel-eluting stents in the first quarter of 2003. The choice of stenting strategy was at the operator's discretion: T-stenting, Coulotte, kissing, or crush stenting. All patients were evaluated for MACE (ie, death, acute myocardial infarction, or target vessel revascularization [TVR]) (Figure 9). Nine month follow-up in patients treated during the TAXUS stent period showed them to have roughly twice the MACE rate seen in patients treated with CYPHER stents (P = 0.03). There were also differences in stenting technique between the 2 groups, and larger studies with more complete angiographic follow-up are needed to establish whether there are significant differences in outcome between the 2 stent systems in bifurcation settings.

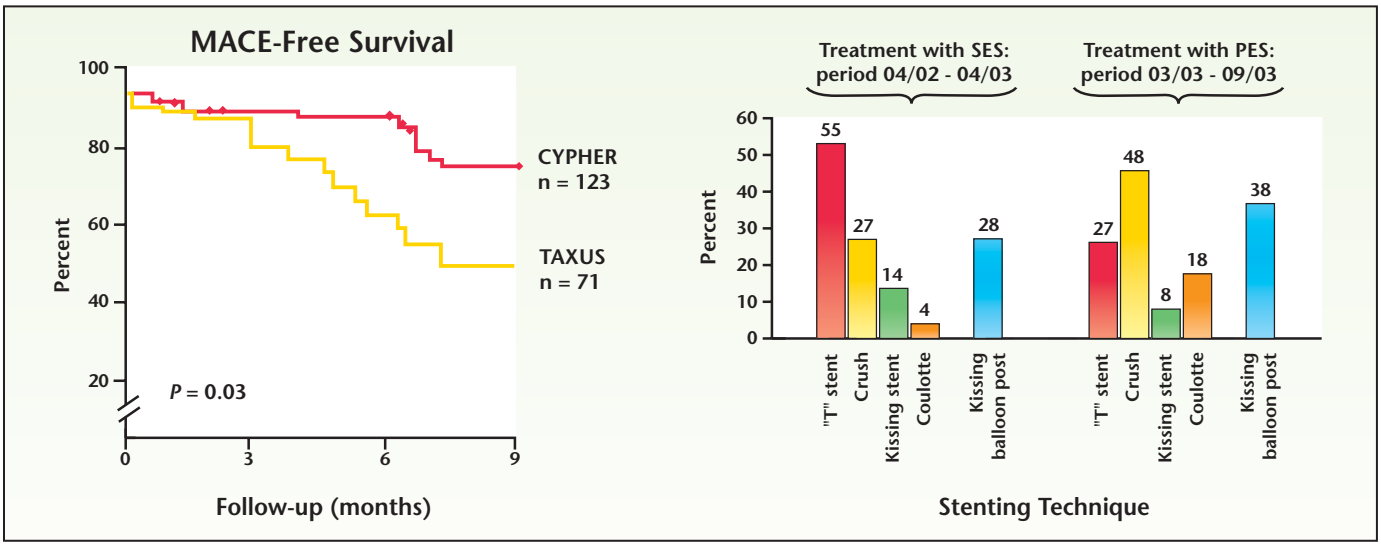


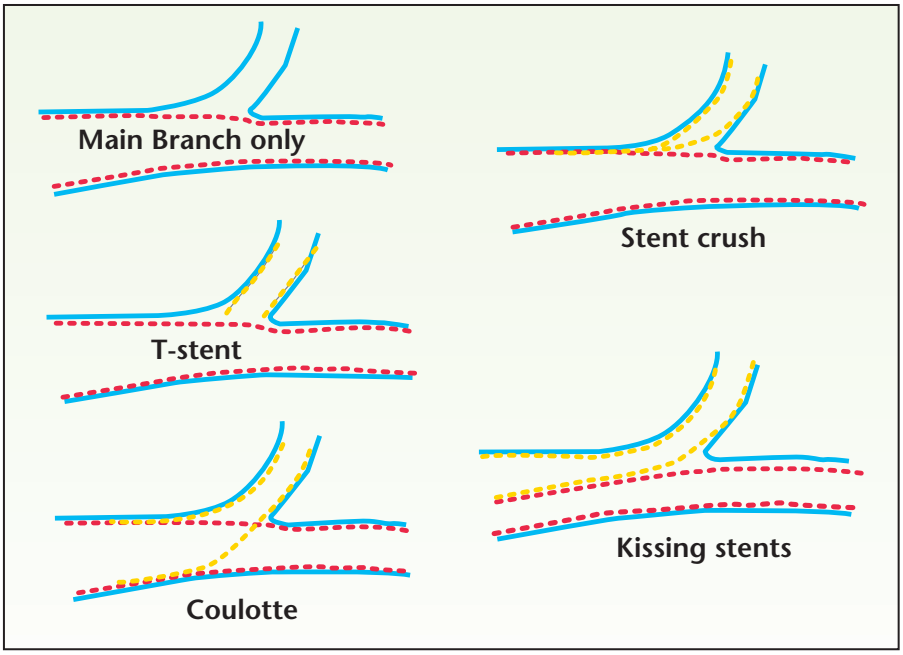
Figure 9. *Major adverse cardiac events and stenting techniques in a consecutive series of patients with de novo lesions treated with drug-eluting stent implantation (SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent) in both the main vessel and side branch. Reprinted with permission from Hoye et al.*[30]

Of even greater interest is whether one can construct a stent specifically designed for bifurcation settings. There is little doubt that bifurcations respond differently to stent implantation. The degree of injury caused by stenting at sites of bifurcation may be much greater than in regular coronary vessels due to differences in elastin content and structure. It is possible that the relationship between the degree of injury caused to elastin and the degree of tissue responses, described by Schwartz and colleagues over a decade ago, may be dramatically accentuated in settings of bifurcation.[18]

A second essential difference at settings of bifurcation is variation in flow patterns. Recent studies have demonstrated that flow disturbances at settings of bifurcation may alter biological responses to intervention such as acute leukocyte recruitment and the pattern of neointimal hyperplasia.[31] They may also lead to differential rates of drug release from stents or drug retention in vascular tissues after deposition.

Various technical approaches have been proposed for treating bifurcations with currently available drug-eluting stents. Favored approaches are shown schematically in Figure 10 and range from main branch only stenting to crush stenting and kissing stents, T stenting and Coulotte stenting. The optimal solution to this challenging setting may well lie in stents designed specifically for bifurcation settings, which will provide optimal strut coverage and drug delivery to all aspects of the

Figure 10. *Schematic representation of how stent struts are delivered to the main vessel, as well as the side branch ostium, using currently favored approaches for treating bifurcations. Note that complete coverage of the side branch ostium as well as the main vessel is difficult to achieve with use of tubular stents in any of these configurations.*



main vessel and its side branch.

Acute Myocardial Infarction Stenting

There is ever-broadening use of stenting to treat patients suffering from acute ST-segment elevation myocardial infarction (STEMI). The role of drug-eluting stents in this setting is in evolution, but the long-term limitation of restenosis after bare metal stent implantation is no less an issue in this setting than in others. The RESEARCH registry[32] has published outcomes after CYPHER stenting in STEMI patients, with good long-term results and, importantly, no evidence of subacute stent thrombosis (0/186 patients). In contrast, the same group recently reported, from the T-Search registry,[33] a 4% stent thrombosis rate among 100 patients with STEMI treated with TAXUS stents. Larger registry or direct comparative studies will be required to confirm the suggestion from these initial reports that there may be higher risks of subacute stent thrombosis with paclitaxel elution than with sirolimus elution, in the already highly thrombotic STEMI milieu.

Conclusions

The drug-eluting coronary stent represents a major advance in the treatment of patients with coronary artery disease. However, important differences exist among stent designs, drug-delivery vehicles, and choice of pharmacologic agents. Additional studies under real-world conditions are needed to determine the ideal combination of system components in various patient and lesion subsets such as diabetes, small vessels, long lesions, diseased saphenous vein bypass grafts, etc. For some of these, current devices may be ideal, whereas for others, future device generations with novel drugs, stent designs, or release modalities may be required. ■

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Main Points

- A rational therapeutic approach to preventing restenosis is the use of drugs that interfere with the biological processes involved in the development of neointimal hyperplasia. Local drug delivery via stents results in minimal systemic exposure and decreased risk of toxic drug effects.
- Sirolimus is an immunosuppressant with both anti-inflammatory and antiproliferative properties that interfere early in the cell cycle, inhibiting the passage of cells from the G1 to the S phase. Drugs that inhibit the cell cycle in the G1 phase are considered cytostatic and may be less toxic than drugs that act later in the cell cycle.
- Paclitaxel promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization, resulting in the inhibition of the normal dynamic reorganization of the microtubule network. It induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis, thereby halting the cell cycle during the M phase.
- Stent-based drug delivery can be accomplished via several different drug/polymer assembly strategies that encourage an even and continuous release of drug. These include the matrix and reservoir techniques, systems that combine both of these techniques, and a design option avoiding the use of a polymer, where an antiproliferative drug is bound to the surface of the stent or embedded within the macroscopic fenestrations.
- A polymer/drug coating applied to a stent with an open cell design might potentially achieve inadequate dosing on the outer curvature, where the struts are widely spaced, and toxic dosing on the inner curvature, where the struts are closer together, whereas a closed cell design stent theoretically allows for uniform dosing in all areas of the lesion.
- Several studies comparing the CYPHER and TAXUS stent systems (the two drug-eluting stent systems currently approved for use by the USFDA), in "workhorse" lesions as well as several specific lesion and clinical subsets, are underway, as are studies of the Endeavor ABT578-eluting stent, and the Challenge and Xience everolimus-eluting stents.
- Real-world complications in the use of drug-eluting stent systems, which require further study, include scenarios of overlapping stents, stenting of bifurcation lesions, and stenting in the setting of acute myocardial infarction.

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