Drug-Eluting Stents

Current clinical experience and future directions.

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In the past decade, the introduction of stents in the treatment of coronary artery lesions led to a significant improvement of both clinical and angiographic outcome in a broad variety of lesion subsets. To date, stents have been established as a gold standard. However, lumen renarrowing due to tissue proliferation within the stented segment has emerged as a major limitation of this treatment strategy. The broad acceptance and frequent use of stents has made their associated restenosis rates a relevant problem. Therefore, current clinical research in interventional cardiology is particularly focused on finding new approaches to reduce, or eliminate, the proliferative vessel response.

Recently, drug-eluting stents have been introduced as a new promising technique to address this issue effectively and, to date, this strategy has changed clinical practice. Coated with antiproliferative agents, these stents provide both a mechanical, as well as a biochemical approach to inhibit recurrent lumen renarrowing. Drug-eluting stents are able to influence vessel recoil, vessel remodeling, and intimal proliferation at once, which are the main factors responsible for restenosis.

In contrast to bare-metal stents, modern drug-eluting stents are complex three-component systems consisting of a stent platform, the drug-carrier vehicle, and the drug itself. A wide variety of possible modifications of these three components is the reason for the many types of different stent designs. These designs have been, and will be, tested in preclinical and clinical studies in order to find the most optimal design for treatment of coronary artery disease by stent-based local drug delivery.

ESTABLISHED AND NEW DRUGS

Sirolimus and paclitaxel, two antiproliferative agents proven to be effective in other therapeutic areas, were the first drugs under clinical investigation in the field of stent-based intracoronary applications.

Macrocyclic sirolimus acts as a immunosuppressive and antiproliferative binding to specific cytosolic immunophilins. It blocks G1 to S cell cycle progression and thereby prevents proliferation of T cells, as well as the proliferation and migration of smooth muscle cells.

Paclitaxel is an antineoplastic agent that has already been used in cancer treatment, primarily against breast and ovarian cancer. It is highly lipophilic, which promotes a rapid cellular uptake. Paclitaxel interferes with microtubule function, affecting mitosis and extracellular secretion, and thereby interrupts the restenotic cascade at multiple levels. In vitro tests show a dose-dependent cytostatic inhibition of smooth muscle cells with therapeutic concentrations of paclitaxel.

Both agents have been demonstrated to be beneficial in treating coronary lesions due to a significant reduction of intimal proliferation after stent implantation as compared to conventional bare-metal stents with similar safety results (sirolimus: RAVEL, SIRIUS, E-SIRIUS; paclitaxel: TAXUS I, II, III, IV, VI).

Although sirolimus-eluting stents represent a homogeneous group using one single device (Cypher), paclitaxel-eluting stents represent a group of different devices basically divided into nonpolymer- and polymer-based stent designs. In contrast to the successful Taxus stent program, other non-Taxus paclitaxel/paclitaxel-derivative

TABLE 1. DRUG CANDIDATES FOR STENT-BASED CORONARY APPLICATION

Anti-Inflammatory Immunomodulators	Antiproliferative	Migration Inhibitors ECM-Modulators	Promote Healing & Re-Endothelialization
Dexamethasone	QP-2, Taxol	Batimastat	BCP671
M-prednisolone	Actinomycin	Prolyl hydroxylase inhibitors	VEGF
Interferon g-1b	Methothrexate	Halofuginone	Estradiols
Leflunomide	Angiopeptin	C-proteinase inhibitors	NO donors
Sirolimus	Vincristine	Probucol	EPC antibodies
Tacrolimus	Mitomycine		Biorest
Everolimus	Statins		Advanced coatings
Mycophenolic acid	C MYC antisense		
Mizoribine	Abbott ABT- 578		
Cyclosporine	RestenASE		
Tranilast	2-chloro-deoxyadenosine		
	PCNA Ribozyme		

studies have been stopped prematurely (ie, SCORE) due to an unacceptable safety profile of the specific stent design; others did not yield sufficient clinical benefit to justify commercialization of the device (ie, DELIVER I and II).

Today, new drugs have been introduced into clinical testing (Table 1). Currently promising candidates for new drug-eluting stent systems are sirolimus derivatives, such as everolimus, ABT-578, and biolimus.

Everolimus

Everolimus, like rapamycin, blocks growth factor-derived cell proliferation, arresting the cell cycle at the G1 to S phase. It does not inhibit the synthesis of growth factors, but blocks growth factor-driven signal transduction in the cellular responses to alloantigens. After preclinical animal studies that demonstrated excellent safety and efficacy of this new device, the clinical FUTURE program has been started. FUTURE I and II were designed to demonstrate safety and feasibility of the everolimus-eluting stent in a small patient population with focal *de novo* coronary lesions. At follow-up, an acceptable safety profile without evidence of stent thrombosis or late stent malapposition was observed. Moreover, these studies revealed a remarkable reduction of neointimal proliferation after everolimus-eluting stent implantation as compared to bare control stents. Two pivotal trials are planed (FUTURE III and IV) to demonstrate the efficacy of this stent design, especially in comparison to the already approved drug-eluting stent systems with the noninferiority FUTURE IV study.

ABT-578

ABT-578 is a new synthetic analogue of rapamycin. It is a potent antiproliferative and anti-inflammatory agent with a broad therapeutic window, allowing biologic effects at low concentrations. ABT-578 is structurally different from sirolimus through the substitution of a tetrazole ring at the 42- position. ABT-578 inhibits the cell cycle in the late G1 phase. The cellular target molecule is FKBP. ABT-578 inhibits the mTOR regulatory protein, resulting in a sufficient block of the common pathway for growth factor stimulation. Given these pharmakodynamics, ABT-578 was considered beneficial for intracoronary delivery to arrest the process responsible for neointimal hyperplasia after angioplasty and stenting. Consequently, the ABT-578-eluting Endeavor stent system was created, representing a potential new alternative for treating patients with coronary heart disease. To evaluate safety, feasibility, and efficacy of this stent design, the ENDEAVOR clinical program has been started, including three randomized clinical trials. ENDEAVOR I is the first-in-man trial including 100 patients with native *de novo* coronary lesions. The 4-month follow-up data, recently presented, demonstrated safety and feasibility of this new drug-eluting stent concept with a 4-month MACE rate of 2%. To evaluate this stent system in a larger patient population, as well as more complex lesion subsets, the mul-

TABLE 2. OVERVIEW ON RANDOMIZED DRUG-ELUTING STENT STUDIES

Study	Drug	LL in-stent	LL in-segment	RR in-stent	RR in-segment	MACE
RAVEL	Sirolimus	-0.01	-0.05	0%	0%	5.8% (12mo)
SIRIUS	Sirolimus	0.17	0.24	3.2%	8.9%	4.9% (9mo)
TAXUS II slow release	Paclitaxel	0.31	-	2.3%	5.5%	8.4% (6mo)
TAXUS II moderate release	Paclitaxel	0.30	-	4.7%	8.6%	7.8% (6mo)
TAXUS IV	Paclitaxel	0.39	0.23	5.5%	7.9%	8.5% (9mo)
TAXUS VI	Paclitaxel	0.39	0.24	9.1%	12.4%	16.4% (9mo)
DELIVER I	Paclitaxel	0.81	0.43	14.9%	16.7%	6.6% (9mo)
ASPECT low dose	Paclitaxel	-	0.57	-	12%	5/13%
ASPECT high dose	Paclitaxel	-	0.29	-	4%	4/33%
ELUTES low dose	Paclitaxel	-	0.72	-	20%	3% (6mo)
ELUTES high dose	Paclitaxel	-	0.10	-	3%	11% (6mo)
FUTURE I	Everolimus	0.11	0.19	0%	4.0%	7.7% (6mo)
FUTURE II	Everolimus	0.12	0.16	0%	4.8%	4.8% (6mo)
ENDEAVOR I	ABT-578	0.33	0.20	-	3.3%	2% (4mo)
ACTION low dose	Actinomycin	1.02	-	25%	-	18.3% (6mo)
ACTION low dose	Actinomycin	0.93	-	17%	-	28.1% (6mo)
SCORE	QP-2	-	0.34	-	7.4%	31.7% (12mo)

ticenter study ENDEAVOR II has been started, including a total of 1,200 patients. The enrollment of this study was completed in January 2004. The aim of the US multicenter study ENDEAVOR III is a head-to-head comparison of the Endeavor ABT-578-eluting stent system with the already approved sirolimus-eluting Cypher stent in 369 patients.

Biolimus A9

Biolimus A9, a new drug, is an analogue of sirolimus (rapamycin), possessing immunosuppressive and antiproliferative properties. Similar to sirolimus, biolimus A9 binds to the cytosolic immunophilin FKBP12 to inhibit growth of T cells and smooth muscle cells. In contrast to sirolimus, biolimus is more rapidly absorbed by the vessel wall. The STEALTH study was conducted to evaluate both safety and efficacy of the new Matrix stent, which is coated with biolimus A9 and a biodegradable polymer as the drug carrier. The trial is still ongoing.

Beyond these single drug stent concepts, a new future approach in the field of drug-eluting stents might be a combination of drugs rather than the elution of a single active agent. One potential combination might be a cell cycle inhibitor with a vasculoprotective agent that promotes healing and stent endothelialization. Specific systems providing directional drug release, so that a cell cycle inhibitor is released on the abluminal side of the stent to travel into the vessel wall, while a different drug is released on the luminal side to promote endothelialization, are currently under development. New polymers with estrogen and nitric oxide release to improve endothelial function have already been tested, with beneficial results.

ESTABLISHED AND NEW COATINGS

In order to create a drug-eluting stent system, the drug must be placed onto the stent surface. Basically, the drug is either placed directly onto the stent or the drug is carried by an additional delivery vehicle. With use of a delivery vehicle, it is possible to control the release kinetics of the loaded drug to guide the drug effect within the vessel wall. However, this additional coating must be biovascularly compatible, without causing any proliferative vessel reaction, delayed endothelialization, or prothrombotic effects itself.

The impact of using a suitable polymer for controlled

drug release versus not using a polymer and placing the drug directly onto the bare-metal stent surface has been nicely demonstrated by the TAXUS and DELIVER studies. Whereas the TAXUS trials revealed a striking benefit of the TAXUS stent, the paclitaxel stent used in DELIVER was not effective enough to meet the study's primary and secondary endpoints.

The reason for the different outcomes is the design of these specific drug-eluting stent concepts. With the non-polymer system tested in DELIVER, paclitaxel is released relatively quickly. *In vitro* studies indicate that 40% of the drug is lost during stent delivery, and the remainder elutes during the next 1 to 2 weeks. With the polymer-based matrix system (Taxus), the polymer allows for a controlled prolonged drug release up to 4 weeks.

New drug-eluting stent systems currently in preclinical and clinical testings use noninflammatory biodegradable polymers that can be formulated to release drug over a longer time period, leaving the bare-metal stent in the vessel wall after a defined period beyond the wall healing time frame.

Another alternative coating has been utilized in the ENDEAVOR trial program; the drug-eluting stents have been coated with phosporylcholine as the drug carrier vehicle. This on-strut phosphorylcholine (PC) coating is a synthetic copy of the predominant phospholipid of the outer red blood cell membranes, resulting in a high biovascular compatibility. In animal studies, PC-coated stents showed significantly less platelet adhesion compared to uncoated stents without affecting (delaying) neoendothelialization. Within 5 days, more than 90% of the PC-coated coronary stent had been re-endothelialized.

Additional new promising future coatings might consist of active components, such as the currently tested endothelial progenitor cell capture coatings that promote the vessel healing process. Liposomal bisphosphonate coatings might be able to inactivate macrophages and inhibit intimal hyperplasia as a more physiologic solution to restenosis.

ESTABLISHED AND NEW STENT PLATFORMS

Despite the need for sufficient drugs and drug carrier vehicles, even drug-eluting stents are based on stent platforms. Presently, these platforms are mainly commercially available conventional bare-metal stents. However, to ensure a controlled drug effect, several design aspects need to be considered in the platform development process, more importantly now than in the past. For instance, there should be only minimal gapping with optimal spatial coverage for uniform drug delivery and distribution. A closed cell design more than an open cell stent ensures that the drug is appropriately targeted along the entire stented site. Stent-to-vessel wall contact is crucial for drug delivery.

Numerous new platforms, such as ultra-low–profile, thin-strut stents built from cobalt chromium and other novel materials, may reduce vascular injury and improve deliverability. One unique design incorporates multiple drug reservoirs within stent struts to allow increased drug loading and controlled release.

The first completely biodegradable stent design is presently under preclinical and clinical investigation and might be the future of interventional stenting.

SUMMARY

Drug-eluting stents have entered the arena and, more importantly, changed the landscape of interventional cardiology. Today, we can say that in treating de novo lesions, drug-eluting stents reduce restenosis rates to under 10%, with very acceptable MACE rates. The low restenosis rates of drug-eluting stents have been documented in different trials, with different delivery systems and stent designs, different carrier matrices, and moreover, different drugs and drug kinetics. In RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, and TAXUS I, II, IV, VI, the restenosis rate ranged from 0% to 9%, demonstrating a sufficient antiproliferative effect using this treatment strategy (Table 2).

Despite initial problems with stent thrombosis that could be solved with modified antiplatelet regimens and optimized stent designs, the use of modern drug-eluting stents that are currently commercially available (Cypher, Taxus) has now been proven safe, reliable, and very effective. Because of the complex design of a drug-eluting stent, there are many ways to modify their characteristics by choosing different and new drugs, different and new coatings, as well as different and new stent platforms. Future developments in the field of coronary drug-eluting stents will certainly further impact the practice of both cardiovascular bypass surgery and interventional cardiology. ■

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