Advances in Interventional Cardiology

Drug-Eluting Stent Update 2007

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A nalist projections for the drug-eluting stent (DES) market estimated that the total number of DES implanted in 2010 would go beyond 4.5 million worldwide. Although the initial results seemed promising, longer-term follow-up in a broader range of patients revealed some pitfalls. Delayed neointimal growth, enhanced platelet aggregation, a local hypersensitivity reaction against the polymer coating, stent fracture, and a failure of sirolimus-, paclitaxel-, and tacrolimus-eluting stents to reduce neointimal hyperplasia at 90 and 180 days in animals, when the drug was completely eluted from the stent, are just several examples.1–8

The number of stents currently under investigation is substantial. They are all loaded with drugs that interfere with pathways in the process of inflammation and neointimal proliferation. However, the process of restenosis is a sequence of complex events that has been only partly elucidated over the last 2 decades.9 Locally acting DES provide the opportunity to interfere with the various mechanisms responsible for each step in the restenotic cascade, and a wide variety of different agents are currently available. Although only sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have received US Food and Drug Administration (FDA) approval to date, multiple alternative devices are attempting to find their way to achieve the same goal, namely a reduction of restenosis and the need for repeat interventions.

Established and Investigational Drugs
Six Limus family–related drugs are currently being studied in DES, namely sirolimus, everolimus, biolimus A9, zotarolimus, tacrolimus, and pimecrolimus. Sirolimus, everolimus, biolimus A9, and zotarolimus all bind to the FKBP12 binding protein, which subsequently binds to the mammalian target of rapamycin (mTOR) and thereby blocks the cell cycle mainly of the smooth muscle cell from the G1 to S phase. The mechanisms of action of tacrolimus and pimecrolimus are different. Both drugs bind to FKBP506. The tacrolimus/pimecrolimus FKBP506 complex subsequently inhibits the calcineurin receptor, which leads to decreased cytokine expression on the cell surface membrane and results in an inhibition of T-cell activation and lower smooth muscle cell selectivity (Figures 1 and 2).

A non-Limus family–related drug widely studied for its efficacy in coronary stents is paclitaxel. Its effect has been mainly explained by its ability to stabilize microtubules and thereby inhibit cell division in the G0/G1 and G2/M phases.

Sirolimus
The first of the Limus family drugs used on endovascular prosthesis was sirolimus, a natural macrocyclic lactone that is able to inhibit mTOR.10,11 Sirolimus proved to possess potent antiproliferative and immunosuppressive effects. Several successive studies proved the efficacy of the SES (Cypher, Cordis Corp, Warren, NJ), a polymer-coated bare metal Bx Velocity (Cordis Corp) balloon expandable stent, in populations that ranged from highly selected patients with single lesions to unselected all-comers.12–18 The Cypher stent was the first DES to receive both Conformité Européenne (CE)-mark and FDA approval in April 2002 and 2003, respectively (Figure 3). Because of the polymer, 75% of the drug is slowly released over the first 10 days. Nevertheless, the antirestenotic properties of the SES proved to persist much longer.19 Because there was no significant change in neointimal thickening between 2 and 4 years in the First in Man (FIM) trial and given the continued clinical superiority of SES after 4 years in a pooled analysis of the 4 pivotal randomized Cypher trials (RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions [RAVEL], SIROImUS-coated Bx Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions [SIRIUS], Canadian [C]-SIRIUS and European [E]-SIRIUS), it seems reasonable to rule out a late catch-up in restenosis; at least so far, because both the clinical and angiographic end points continue to slowly accrue over time.14,20

Everolimus
A second derivative of the Limus family is everolimus, a sirolimus analog with a single minimal alteration in its
molecular structure (position 40), without a chemical modification of the mTOR binding domain (Figures 1 and 2). Of interest is that, when implanted in rabbit iliac arteries, a more rapid endothelialization was observed in the everolimus-eluting stent as compared with sirolimus-, zotarolimus-, or paclitaxel-eluting stents, demonstrated by a complete endothelialization of the struts with exhibition of CD31 (antigen surface marker of good endothelial functionality) in the cells at 14 days (R. Virmani, MD, unpublished data, 2006).

The Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions First (SPIRIT) trial proved the superiority of everolimus embedded on a durable polymer on a cobalt chromium stent as compared with bare metal stents (BMS). In the recently completed SPIRIT-II trial, the everolimus-eluting XIENCE V stent (Advanced Cardiovascular Systems, an Abbott Vascular Company, Santa Clara, Calif) proved to be superior to the PES for reduction of both late loss and binary restenosis. Subsequently, the SPIRIT-III trial has randomized 1002 patients in the US to treatment with either an everolimus XIENCE V stent or a PES. As part of the SPIRIT-III study, additional patients will also be enrolled in 4 registry arms in Japan, 1 each for stents that are 38 mm, 2.25 mm, and 4.0 mm long. Additionally, the SPIRIT-IV and SPIRIT-V studies will provide further clinical data.

Zotarolimus
A third descendant of the Limus family, also with a change on position 40, that is used on coronary stents is zotarolimus (ABT-578, Abbott Pharmaceuticals, Abbott Park, Ill), which likewise contains antiproliferative and antiinflammatory effects, but zotarolimus is suggested to have higher tissue retention compared with the SES (Figures 1, 2). Of note, recent data on endothelial function after stent placement in porcine coronaries showed a normally functioning endothelium 1 and 3 months after zotarolimus-eluting stent implantation, whereas a dysfunctional endothelium was observed after both Cypher and Taxus implantation.

In the ENDEAVOR I and II trials, the phosphorylcholine polymer-based cobalt-alloy Driver coronary stent (Medtronic Vascular, Santa Rosa, Calif), loaded with zotarolimus, proved to be superior to BMS in both angiographic and clinical end points. Recently presented 2- and 3-year follow-up data of the ENDEAVOR I and II trials proved sustained superiority in the reduction of target lesion revascularization (TLR) with remarkably low rates of total stent thrombosis (0.3%) and no cases of stent thrombosis after 30 days. The ENDEAVOR III trial was a prospective randomized comparison of the Endeavor zotarolimus-eluting stent and the SES (n=436). At 8 months, the Endeavor stent failed to meet its noninferiority end point in terms of late lumen loss. Of note, the rates of death, myocardial infarction, and target vessel...
revascularization were equal in both groups.\textsuperscript{28} A possible explanation for the lack of noninferiority of the Endeavor stent might be the rate of elution. The Cypher stent elutes 75\% of its drug within the first 10 days; in the Endeavor stent this took only 2 days.

Another zotarolimus-eluting device is the Zomaxx Tri-Maxx stent (Abbott Pharmaceuticals, Abbott Park, Ill.), which has a trilayer pharmacoat that consists of a phosphorylcholine basecoat and topcoat wrapped around a zotarolimus layer with elution rates comparable to the Cypher stent. The platform used was a stainless steel/tantalum/stainless steel triplex stent. Although the 4-month results of the Zomaxx-IVUS trial (n/H1100540), which showed a late loss of 0.20 mm, were promising, its manufacturer Abbott recently announced it would discontinue the Zomaxx program after the disappointing results of the Zomaxx-I trial. At 9 months, the Zomaxx stent was associated with a significantly higher late loss and binary restenosis rate compared with the Taxus stent.\textsuperscript{29}

**Biolimus**

Biolimus A9 is a highly lipophilic sirolimus analog that inhibits T cell and smooth muscle cell proliferation (Figures 1 and 2). The Stent Eluting A9 Biolimus Trial in Humans (STEALTH) trial was the FIM study to assess the safety and efficacy of the poly-lactic acid bioabsorbable-polymer-coated Biolimus A9–eluting BioMatrix stent (Biosensors International, Singapore). A stainless steel S-stent was the basis for a biodegradable polymer coating that released its drug gradually over 6 to 9 months. The STEALTH-I trial randomized 120 (1:2) patients to treatment with a control bare metal S-stent or a Biolimus A9–eluting stent. Although the 12-month clinical event rates were similar between both groups, treatment with the Biolimus A9 stent was associated with a 57\% lower rate of binary restenosis and 65\% lower rate of late lumen loss compared with the BMS group at 6 months.\textsuperscript{30} The recently presented 9-month results of the Nobori-I trial, which randomized (2:1) patients to either a PES (n/H1100535) or the Biolimus-eluting stent (n/H1100585), showed significantly less late lumen loss in the Biolimus arm as compared with the Taxus arm.\textsuperscript{31}

**Pimecrolimus**

Although a part of the Limus family, pimecrolimus does not block mTOR and inhibits to a much lesser degree the endothelial cell proliferation (Figures 1 and 2).\textsuperscript{32} The active pharmaceutical ingredient of pimecrolimus is Elidel, an FDA-approved drug developed by Novartis Pharmaceuticals Corp, East Hanover, NJ for the treatment of atopic dermatitis. The FIM study to evaluate the safety and efficacy of a pimecrolimus-eluting stent is currently ongoing.\textsuperscript{33}

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**Figure 2.** Molecular structure of sirolimus, everolimus, biolimus, zotarolimus, tacrolimus, and pimecrolimus.
Tacrolimus

Tacrolimus (FK506) is a water-insoluble macrolide immunosuppressant produced by streptomyces tsukubaensis (Figures 1 and 2). Tacrolimus is also known as Prograf, a drug widely used to prevent allograft rejection after organ transplantation. Tacrolimus is a noncytotoxic T cell inhibitor, which holds cells in the G0 or resting phase. In this situation, cells are able to function but unable to replicate. The end result of tacrolimus is a reduction in activation of cytokine genes. In contrast to sirolimus, tacrolimus demonstrates far more potent inhibition of smooth muscle cells rather than endothelial cells.4,34

The multicenter European Direct Stenting of De Novo Coronary Artery Stenosis With Tacrolimus-Eluting Versus Carbon-Coated Carbostents (JUPITER)–II trial (n/H11005332) was conducted to compare the safety and effectiveness of direct stenting with a Janus tacrolimus-eluting stent (Sorin Biomedica Cardio, Saluggia, Italy) versus the mechanical platform with no drug-eluting capability from which the Janus stent (Tecnic CCS coronary carbostents) was derived. In the Janus tacrolimus-eluting stent, the drug is embedded in reservoirs carved on the outer stent surface to release the drug only toward the vessel wall and possesses an integral thromboresistant carbofilm coating on the whole stent surface. Remarkable was that at 1 year no cases of stent thrombosis were reported in the polymer-free tacrolimus-eluting stent arm. However, the 6-month in-stent late lumen loss of 0.65 mm for the Janus was equal to the Tecnic carbofilm stent; therefore the study failed to meet its primary end point.35 The currently ongoing 3-arm Inova trial is evaluating the efficacy of a Janus Carbofilm–coated SRT stent platform with different formulations of tacrolimus: (1) pure tacrolimus (3.3 μg/mm²); (2) tacrolimus with 20% ascorbyl palmitate (2.3 μg/mm²); (3) tacrolimus with 20% PVP Kollidon 17 (2.3 μg/mm²). Along these lines, the Japanese company Kaneka is evaluating the efficacy of a tacrolimus when applied on a cobalt chromium platform with a poly-DL-lactide-coglycolide biodegradable polymer.

Paclitaxel

Although not a member of the Limus family, the PES (Taxus, Boston Scientific, Natick, Mass) was the second DES to receive FDA approval, 1 year after the SES. Paclitaxel was first found by The National Cancer Institute in a search for naturally occurring agents with strong antiproliferative qualities. Paclitaxel stabilizes microtubules and thereby inhibits cell division in the G0/G1 and G2/M phases (Figure 1). The randomized TAXUS-I trial (2003) was designed as a FIM phase I feasibility study and proved that a polymer-coated PES was superior to BMS at 6 and 12 months of follow-up.36 Thereafter, the TAXUS family trials expanded with the II, IV, V, and VI trials and confirmed the superiority of PES as compared with BMS in more complex patients and lesions.36–39 Recently, the TAXUS-V-ISR (in-stent restenosis) trial compared the efficacy of a slow-release polymer-based PES with brachytherapy for in-stent restenotic lesions. At 9 months, the use of PES was associated with lower rates of clinical and angiographic restenosis and an improved event-free survival.40 The TAXUS clinical trial program, which assessed the TAXUS Express stent system from single to complex lesions, was followed by the TAXUS ATLAS and Olympia programs, which transferred the established polymer drug combination to a new stent platform, the Liberté stent.41,42

Another new device coated with paclitaxel is the Asian Infinnium (Sahajanand Medical Technologies, Gujarat, India) stent. The stent has a biodegradable hemocompatible polymer

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**Figure 3.** CE or FDA approval of current and investigational devices.
coating and lower strut thickness (0.084 mm compared with 0.14 mm for Cypher) designed to reduce vessel trauma. The coating consists of slow, medium, and fast release polymer layers. The multicenter open-label registry Safety and Efficacy of Infinium: A Paclitaxel-Eluting Stent (SIMPLE-I) trial (n=282) was the first to test the efficacy of this new device. The SIMPLE-I trial was followed by the multicenter, single-arm, prospective SIMPLE-II trial (n=103) to further investigate the safety and the efficacy of the Infinium stent.43 With little late loss at 6 months (0.38 mm) and a binary restenosis rate of 7.3%, the device was the first indigenously designed and evaluated “low-cost” DES from Asia to receive CE mark approval.

**New Coatings**

After disappointing results with the use of carbon-, platinum-, and gold-coated stents, the polymer was hypothesized to be an appealing alternative carrier to reduce restenosis and thrombosis and to guarantee controlled drug-release kinetics.44 Soon, the first-generation polymer-coated SES and PES proved to be more effective than their non–polymer-coated counterparts.45–48 Nevertheless, a major limitation is that many polymer coatings are not entirely inert, and hypersensitivity reactions against the polymer have been frequently reported.1,3,49 In line with this data, long-term adverse effects such as increased inflammation of the vessel wall, a thrombogenic response, and induced apoptosis of smooth muscle cells have been described.50,51

To reduce the inflammatory reaction, which is partially caused by the polymer, Medtronic recently developed a novel co-polymer, the “Endeavor Resolute”, for extended release of zotarolimus in a next-generation DES. The new BioLinx polymer system contains a C10 polymer, which is lipophilic/hydrophobic and stimulates a controlled drug release, a C19 polymer, which is primarily hydrophilic and thus more biocompatible and helpful in drug elution, and finally polyvinyl pyrrolidone, which is hydrophilic, increases the initial molecular weight of the polymer and the number of unstable linkages. Furthermore, the drug-release profile can be adjusted by alteration of the biodegradation profile of the polymer.

**New Platforms**

Several limitations and side effects have been associated with coronary stenting. First, stents cause permanent physical irritation with the risk of long-term endothelial dysfunction or inflammation.5 Second, stents possess a high thrombogenicity.56 Third, stents create an inability for the vessel to remodel and act in a normal physiological way.5 Finally, stents create difficulties for possible future bypass surgery and noninvasive imaging. The first bioabsorbable stents were made of poly-L-lactic acid and recently studied in porcine models.57 The first successful in-human experience with a poly-L-lactic acid stent was described by Tamai et al in 2000.58 The study included 15 patients treated with a monopolymer poly-L-lactic acid Igaki-Tamai stent (Igaki Medical Planning Co, Ltd, Kyoto, Japan) with a zigzag helical coil pattern. The stent expanded by itself at a temperature of 37°C. Angiographic restenosis rate and TLR was 10.5%, which thereby proved that its use was feasible, safe, and effective in humans.

The 30-day results of the FIM ABSORB trial (n=30) are worth mentioning. The BVS stent (Figure 4) (Bioabsorbable Vascular Solutions, Guidant Corp, Indianapolis, Ind), the world’s first fully absorbable DES, which consists of a bioabsorbable poly lactic acid polymer that contains everolimus (98 μg/cm² of surface area) and a bioabsorbable BVS poly lactic acid stent platform, proved to be associated with a 100% procedural success rate and a major adverse cardiac event rate of 0%. Furthermore, the stent recoil of 6.85% was comparable to the 4.27% seen with the XIENCE V metal stent.59–61
REVA Medical, Inc. (San Diego, Calif) is presently investigating a fully absorbable polymer stent with a “slide & lock” design; sliding parts with monodirectional lockouts that are hypothesized to result in a nearly negligible stent recoil (Figure 5). The stent consists of a radiopaque tyrosine-derived polycarbonate backbone. The composition of the polymer, comprised of 3 basic components, allows the resorption time to be varied by a change in the ratio of these components. Both a bare and a paclitaxel-eluting version, in which the polymer is mixed with the drug, will become available. The Randomized Endovascular Study of the REVA Biodegradable Stent (RESORB) clinical trial has been recently designed to assess the safety of this new platform.

Another alternative for the metallic backbone of the stent was found in magnesium. Magnesium, with antithrombotic, antiarrhythmic, and antiproliferative properties, is one of the first natural body components to be used as a basis for a bioabsorbable stent. Several experimental studies to evaluate the efficacy of a magnesium alloy stent degradable by biocorrosion have been performed. Heublein et al described the use of a coronary stent prototype that consisted of the noncommercial magnesium-based alloy AE21 (contains 2% aluminum and 1% rare earth metals) with an expected 50% loss of mass within 6 months in 11 domestic pigs (Figure 6). Quantitative angiography at follow-up showed a significant 40% loss of perfused lumen between 10 and 35 days caused by the loss of mechanical integrity of the stent.62 One year later, the use of a bioabsorbable magnesium alloy–based stent with a controlled corrosion in 20 patients with critical limb ischemia was described. At 9 months, a 90% vessel patency was observed.63 As a result of the successful FIM trial (n=5) by Erbel and colleagues, the enrollment in the larger worldwide PROGRESS-AMS study has been recently completed.64 The 4-month results showed a late loss of 1.08±0.49 and an ischemia-driven TLR rate of 23.8%, which was comparable to those reported with the use of BMS.

New Concepts

An appealing new concept is the dual DES. In line with the previously mentioned dual-layer heparin-SES, Abbott’s Zodiac program incorporates a trilayer stent that embeds both zotarolimus and dexamethasone. Dexamethasone is a potent antiinflammatory agent that is used for a variety of inflammatory and immune diseases. Glucocorticoids suppress the production and effects of humoral factors involved in the inflammatory response, inhibit leukocyte migration to sites of inflammation, and have a rather low effect on endothelial (≈35%) and smooth muscle cell (≈60%) proliferation.65–68 Although the Study of Antirestenosis With the BiodivYsio Dexamethasone-Eluting Stent (STRIDE) trial, the FIM pilot trial that evaluated the safety and efficacy of a dexamethasone-eluting stent (BiodivYsio Matrix LO stent, Biocompatibles, Ltd., Farnham, UK) demonstrated an acceptable binary restenosis rate of 13.3%,69 the preliminary 6-month results of the larger-scale Drug-Eluting Stents for In-Stent Restenosis (DESIRE) trial showed a clinically driven target
vessel recascularization rate of 9.5%, which was 50% higher than the target vessel recascularization rates in the TAXUS-IV and SIRIUS trials. The final results were never published, and it is to be expected whether the simultaneous inhibition of smooth muscle cell proliferation and endothelial inflammation by zotarolimus and dexamethasone in the Zodiac program will turn out to be successful.

Promising results are also expected from the Randomized, Multicenter Study of the Pimecrolimus-Eluting (Corio) and Pimecrolimus/Paclitaxel–Eluting Coronary Stent System (SymBio) in Patients With De Novo Lesions of the Native Coronary Arteries (GENESIS) trial, which will compare a dual paclitaxel/pimecrolimus-eluting stent with a stent that elutes only pimecrolimus. Additionally, a dual sirolimus/genstein-eluting stent is currently under investigation (Figure 7). Genstein is a potential isoflavone, which possesses dose-dependent antiplatelet and antiproliferative properties and inhibits collagen-induced platelet aggregation responsible for primary thrombosis. The stent consists of 5 layers that contain an alternating blend of sirolimus and genstein and a drug-free top layer. The unique biodegradable heparinized polymer blend includes poly-L-lactide, poly-DL-lactide-co-glycolide and polyvinyl pyrrolidone. A complex elution pattern aims to provide both smooth muscle cell proliferation by sirolimus and short- and long-term thrombus formation by genistein.

The Prohealing Approach

Endothelial progenitor cells have been identified as a key factor in the reendothelialization process after stent implantation. To accelerate the process of endothelialization and thereby reduce the risk of thrombosis and restenosis, the Genous Bioengineered R stent (OrbusNeich, Fort Lauderdale, Fla) was developed. The Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth (HEALING)-FIM (n = 16) was the first clinical study to evaluate the use of an endothelial progenitor cell (EPC)-captured stent, which was developed with immobilized antibodies targeted at EPC surface antigens. Six-month angiographic outcomes showed a binary restenosis rate of 13.3% with an associated late loss of 0.63 ± 0.52. Nine-month outcomes showed that its use was safe and feasible (major adverse cardiac event and cerebrovascular events rate was 6.3%). The HEALING-II study (n = 63) extended these results in a nonrandomized multicenter trial. The initial results reported a zero incidence of major adverse cardiac events at 30 days and 6-month in-stent restenosis rates of 17.2% with an associated in-stent late luminal loss 0.78 ± 0.39. Of interest is the late loss at 18 months, which decreased to 0.59 ± 0.06 mm. Of note, 2 things have to be mentioned. First, the patient’s total number of circulating EPCs were shown to be critical importance for the efficacy of the EPC-captured stent. This can be illustrated by the results of the HEALING-I; late loss in patients found to have low levels of circulating EPCs was more than double that of patients with normal circulating EPC levels. Second, the total number of circulation EPCs can be increased by an optimal usage of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).

Following the dual-elution trend, recent developments have been made on an EPC-DES combination. A concept of a stent with a biodegradable, abuminally focused drug on a Genous-coated platform with an additional drug component integrated throughout the polymer backbone. The stent should be able to enhance drug delivery at the abluminal site, to inhibit neointimal proliferation, and to simultaneously possess CD34 endothelial cell capture activity at the endoluminal site to enhance reendothelialization.

New Techniques of Elution

The Conor Medstent (Conor Medsystems, Inc., Menlo Park, Calif) was the first stent specifically designed for drug-delivery, and it guaranteed an expanded drug capacity and controllable release kinetics. The stent was equipped with hundreds of laser-cut holes, and the drug could be deposited in multilayered degradable polymer inlays. The Paclitaxel in Stent Controlled Eluting Study (PISCES) study was the FIM study to evaluate the safety and potential efficacy of a 316L stainless steel Conor stent system with an erodable polymer with complete elution of low doses of paclitaxel. The study included 6 groups distinguished by different paclitaxel-doses with fast or slow and unidirectional...
or bidirectional release kinetics. At 30 days, the lowest in-stent late loss (0.38 mm and 0.30 mm) and volume obstruction (8% and 5%) were observed in the 10-μg and 30-μg doses groups, respectively, both with unidirectional release.\textsuperscript{75,76} The PISCES study was followed by the Study of Controlled Elution of Paclitaxel for the Elimination of Restenosis (SCEPTER) trial, a safety and effectiveness study intended to justify market clearance in the European Community and incorporate 2 arms of 130 patients.\textsuperscript{77}

The Conor Cobalt Chromium Stent With Antiproliferative for Restenosis (COSTAR)-I trial evaluated the use of an equally effective, more flexible, and more deliverable cobalt chromium COSTAR paclitaxel-eluting coronary stent system. The stent uses a poly-lactic-co-glycolic acid bioabsorbable polymer, limited to the small wells embedded in the stent where the drug is loaded, which thereby leaves the actual stent surface free of polymer.\textsuperscript{78} The small-scale dose-finding COSTAR-I trial (n=87) was directly followed by the European Cobalt Chromium Stent With Antiproliferative for Restenosis (EuroSTAR) trial and the COSTAR-II trial. The EUROSTAR trial showed that the Costar stent system was highly deliverable and radiopaque, and it permitted high rates of acute success and direct stenting. One-year clinical follow-up data showed a 2.8% and 3.4% incidence of TLR in the 10-μg and 30-μg groups, respectively, associated with an in-stent late loss of 0.25 mm and 0.36 mm.\textsuperscript{79} On the basis of these results, the cobalt chromium COSTAR paclitaxel-eluting coronary stent recently received CE mark approval. Furthermore, the deliverability of the stent has proven to be of great importance. With the growing complexity of the lesions treated percutaneously, there exists a need for devices with better deliverability and higher flexibility. For that reason, both the Taxus Liberté (Boston Scientific) and Cypher Select (Cordis) were developed.

To improve the efficacy of stenting of specific lesions like bifurcations, the multicenter Axxess Plus Biolimus Stent in LMCA Bifurcations Trial (AXXENT) registry (n=33), was conducted to evaluate the safety and efficacy of the DEVAX-AXXESS bifurcation stent (Devax, Inc., Irvine, Calif) for use in the left main coronary artery. Procedural success rates have been shown to be high, and with a 30-day major adverse cardiac event rate of 6.1%, the early results looked encouraging.\textsuperscript{80} Recently the DIVERGE trial has been conducted to further assess the efficacy of this specific bifurcation device. Comparable dedicated bifurcation devices are the Multilink Frontier (Abbott),\textsuperscript{81} which was designed to preserve side-branch access; the Invatec system (Invatec srl, Roncadelle, Italy) with axial and rotational self-positioning properties; the Nile CroCo (Minvasys, Gennevilliers, France), which allows instant poststent “kissing balloon” dilatation; the Petal (Boston Scientific) with a side aperture and deployable struts; the Sideguard (Cappella, Inc, Auburndale, Mass), a Nitinol self-

![Figure 6. Light microscopy (A) and scanning electron microscopy (B) images of the magnesium-based alloy AE21 stent.](image_url)
expanding device on a single-catheter delivery system; and the Tryton stent (Tryton Medical, Inc, Newton, Mass).

A promising new concept is the Xtent modular system for long lesions, multiple lesions, and multivessel disease (Figure 8). The Biolimus A9 polylactic acid bioabsorbable polymer-coated stent (Biosensors International) has a modular design and consists of multiple 6-mm cobalt chromium stent segments that are interdigitated, which allows for in situ customization of stent length. The delivery system consists of a balloon that can be shortened and reused during the procedure, which may eliminate the need to use a separate postdeployment balloon and may result in significant device cost savings, reduced catheter exchanges, and shorter procedure times. The device is currently under investigation in the CUSTOM-II trial, which aims to extend the promising results of the CUSTOM-I registry.

Finally, an ultralow-profile, self-expandable, thin strut stent mounted on a guide wire (CardioMind, Sunnyvale, Calif) is in development for specific use in small vessels.

### Current Clinical Results

Although many of the investigated devices have been shown to be effective in the reduction of restenosis and the need for repeat revascularization, drug-coated devices like those coated with batistimat, actinomycin, or tacrolimus, or taxol-dipped stents failed to show superiority compared with BMS.48,82–84 The relative efficacy of the more successful DES cannot be easily assessed because they are most often compared with BMS. Randomized trials such as the Prospective, Randomized, Multi-Center Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems (REALITY), Paclitaxel and Sirolimus Stents in the Real World of Interventional Cardiology (TAXI) study, Drug-Eluting Stent for Complex Lesions: Cordoba–Las Palmas Study (CORPAL), Sirolimus-Eluting Stent Compared with Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTA) study, Intracoronary Stenting and Angiographic Results—Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) trial, and the ISAR-Diabetes trial directly compared SES and PES in a wide variety of patient and lesion types.85–90 The Basel Stent Kosten Effektivitäts Trial (BASKET) assessed the cost-effectiveness of SES and PES combined versus BMS.91 Both the SIRTA and ISAR-DESIRE showed TLR rates that favored SES.88,89 However, the TAXI, REAL-

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Figure 7. Design of the genistein-sirolimus dual-eluting stent. Total drug dose: 2.51 mg/mm² (112 mg genistein and 76 mg sirolimus content on 16-mm stent). Unique biodegradable heparinized polymers blend includes poly-L-lactide, 50/50 poly-DL-lactide-co-glycolide, and polyvinyl pyrrolidone. Elution profile: Initial high dose of genistein for 2 days to prevent platelet aggregation. (Top layer D). Concurrent release of genistein and sirolimus from layer C between 3 to 9 days will target primary thrombus formation and intimal cell proliferation. Slow release of genistein and sirolimus (Layer B) between 10 to 49 days to prevent mainly cell proliferation. Finally, slow release of genistein (Layer A) from 50 to 89 days will prevent late thrombosis up to 3 months.

Figure 8. The Xtent modular system for long lesions, multiple lesions, and multivessel disease. A, 6-mm CoCr segment; 1 device contains 6 to 10 segments (diameters: 2.5, 3.0, and 3.5 mm). B, The delivery system consists of a balloon that can be shortened and reused during the procedure. C, A modular design that consists of multiple 6-mm CoCr stent segments customized to fit the lesion length. D, Biolimus A9 elutes from a polylactic acid bioabsorbable polymer.
ITY, ISAR-DIABETES, and CORPAL studies did not show a significant difference between both devices.85–87.90 Of note, because of a lack of angiographic follow-up, a large reference vessel diameter, and only 50% of randomized patients, the results of the TAXI trial should be interpreted with care. Two recent meta-analyses showed that the use of SES was associated with lower angiographic restenosis rates and a lower incidence of target vessel recirculation as compared with PES.92,93 Of note, no significant differences were found in the incidence of death or myocardial infarction between both groups. Among the PES registries, the TAXUS Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry is worth mention because it was one of the first studies to reflect real-world clinical practice. The recently published 2-year results did not show a significant difference between PES and SES in any of the clinical end points.94 The much larger Strategic Transcatheter Evaluation of New Therapies (STENT) registry also did not show a significant difference between both devices at 6 months in 6659 patients.95

Currently, a variety of trials that compare the Taxus and CYPHER stents to several newcomers are in progress. In the Prospective, Multicenter, Randomized Trial of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease (ZOMAXX-I) (n= 396), which compared the zotarolimus-eluting Zomaxx stent to a PES, the Zomaxx stent was shown to be associated with a significantly higher late loss at 9 months and thereby failed to meet its primary end point.29 The COBalts chromium STent with Anti-proliferative for Restenosis (COSTAR)-II trial, which used the CONOR platform, is an ongoing, prospective, randomized controlled trial that will include ≈2000 patients at 85 international sites that compare the use of the COSTAR stent to a TAXUS stent.78,96,97 Medtronic’s Patient-Related OuTcomes with Endeavor versus Cypher stenting Trial (PROTECT) is currently enrolling 8000 patients to compare the safety and efficacy of the Endeavor zotarolimus-eluting stent to the Cypher stent, with stent thrombosis as one of its primary end points at 3 years.

Also currently ongoing are 2 prospective, randomized, multicenter trials that compare the Biolimus A9—eluting Biomatrix (Biolimus-eluting stent) with a Cypher SES (Limus Eluted From a Durable versus Erodable Stent Coating (LEADERS) trial; n=1700) and to a Taxus PES (Nobori-I study; n=360). The recently presented 9-month results of the Nobori-I showed significantly less late lumen loss in the Biolimus arm as compared with the Taxus arm.31 Finally, the large-scale SPIRIT III, which was designed for further evaluation of the efficacy of the XIENCE V everolimus-eluting stent, has finished enrollment of its randomized arm.

Conclusions

As with any new device in medicine, the applauded 2 pioneer DES Cypher and TAXUS were shown to possess some side effects as well, some of which only arose very recently.

Currently, various innovative DES types are emerging and will become available in the coming years with the intention to avoid the current pitfalls. Abolition of neointimal hyperplasia is no longer the ultimate goal and has been replaced by the development of more biocompatible and bioabsorbable stents that facilitate adequate endothelialization. Recently, the FDA acknowledged a cause of concern for late adverse events after stent implantation and called for long-term monitoring of safety outcome. It is hoped that the testing of possible remedies to the current deficiencies of the first-generation DES will not be paradoxically hindered by more stringent regulatory measures as a penalty for the late recognition of their inherent limitations.

Disclosures

None.

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