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NOVEL BIOABSORBABLE DRUG-ELUTING STENTS – A NEED IN INTERVENTIONAL CARDIOLOGY

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ABSTRACT

The development of stent has been a major advance in the treatment of obstructive coronary artery disease since the introduction of balloon angioplasty. However, neointimal hyperplasia occurring within the stent leading to in-stent restenosis is a main obstacle in the long-term success of percutaneous coronary intervention (PCI). The recent introduction of drug-eluting stents (DES) contributes a major breakthrough to interventional cardiology. Many large randomized clinical trials using DES have shown a remarkable reduction in angiographic restenosis and target vessel revascularization when compared with bare metal stents. The results of these trials also appear to be supported by evidence from everyday practice and noncontrolled clinical trials. However, the expanded applications of DES, especially in treating complex lesions such as left main trunk, bifurcation, saphenous vein graft lesions, or in-stent restenosis, are still under evaluation with on-going studies. With the availability of different types of DES in the market, the issue of cost should not be a deterrent and DES will eventually be an economically viable option for all patients. The adoption of DES in all percutaneous coronary intervention may become a reality in the near future. In this review article, we summarize the recent development and progress of DES as well as compare and update the results of clinical trials.This review focuses on describing next-generation drug-eluting stent systems based on the use of novel coatings and carrier systems developed to enhance DES safety.

KEY WORDS

Drug-eluting stent, percutaneous transluminal coronary angioplasty, in-stent restenosis

INTRODUCTION

Background of drug-eluting stent development

After the advent of cardiac catheterization in the late 1920s and the development of coronary angiographic technology in the late 1950s, balloon angioplasty (BA) was introduced in the mid 1960s. Balloon angioplasty was first applied to the revascularization of the femoral, popliteal, and renal arteries, and was adapted to the coronary arteries in the late 1970s (Forssmann 1929; Dotter and Judkins 1964; Hurst 1985, 1986). There were important limitations of coronary BA, including the risk of uncontrollable plaque disruption and vascular recoil that may lead to periprocedural coronary occlusion and myocardial infarction, and a 20%–40% incidence of restenosis within 6–12 months after successful revascularization, which compromises the longterm prognosis (Miller et al 1999). Various atherectomy techniques such as rotational atherectomy (rotablation), Excimer Laser Coronary Angioplasty (ELCA), and Directional Coronary Atherectomy (DCA) were developed in late 1980s and early 1990s, but these devices did not significantly improve the long-term outcome due to a lack of an impact on restenosis rate (Mueller et al 1995; Karthikeyan

et al 2004). On the other hand, scaffolding metallic mesh, called stent, was developed during the same period to prevent restenosis after BA. The clinical efficacy of stent compared with conventional BA was studied in two landmark clinical trials. The North American Stent Restenosis Study (STRESS) showed a lower angiographic restenosis rate (31.6% vs 42.1%) and a lower target vessel revascularization (TVR) rate (10.2% vs 15.4%) in stent group than in BA group (Fischman et al 1994). The European comparison of balloon-expandable-stent implantation with BA in patients with coronary artery disease by the Benestent Study Group proved a similar, but more impressive, reduction of restenotic rate (22% vs 32%) ($p = 0.02$) and TVR rate (13.1% vs 22.9%) ($p = 0.005$) in stent group compared with BA group (Serruys et al 1994). Based on the result of these two studies, Palmaz-Schatz balloon-expandable stent (Cordis Corp; a Johnson and Johnson Company, Warren, NJ, USA) was approved as the first bare metal stent (BMS) for elective use by Food and Drug Administration (FDA) in 1994 after Gianturco-Roubin coil stent (Cook Inc, Bloomington, IN, USA) was approved as the first BMS for acute closure in 1993 (Mueller et al 1995). However, the sudden occlusion of vessel due to subacute stent thrombosis (SAT) and late in-stent restenosis (ISR) are two major complications that were initially encountered with the widespread use of BMS. Although the SAT rate has been reduced to approximately 1% with adequate antiplatelet therapy (ie, aspirin and clopidogrel), the incidence of ISR is still a hindrance to the long-term success of the stenting procedure (Schomig et al 1996, 1997). When the use of BMS was expanded in the high-risk restenosis groups of patients such as those with small vessel, long and bifurcation lesions, and diabetes mellitus, ISR and TVR escalated to the range of 50%–60% and 30%–50%, respectively (Yokoi et al 1996). Extensive research was carried out in the late 1990s to seek a solution to the problem of ISR. Brachytherapy with insertion of radioactive devices in the coronary artery was initially developed to prevent ISR (Raizner et al 2000). Despite its moderate success, brachytherapy had limitations such as late thrombosis, geographic mismatch, relatively high cost, and requirement of radiation oncologists, which made it unsuitable for widespread and routine clinical practice (Raizner et al 2000). During the period when the brachytherapy was becoming the treatment of choice of in-stent restenosis, clinical trials of drug-eluting stents (DES) demonstrated a pristine outcome with a very high success rate and very low in-stent restenosis rate. DES has now become the mainstream therapy of coronary artery stenosis due to the expected very low rate of in-stent restenosis and brachytherapy has become a thing of the past.

Drug-eluting stents (DES) were primarily conceived to reduce in-stent neointimal formation and therefore minimize the occurrence of restenosis, the major drawback of percutaneous coronary interventions with bare-metal stents (BMS).

The development of DES has been pioneered through a combination of the increased understanding of the biology of restenosis, the selection of drugs that target 1 or more pathways in the restenotic process, controlled-release drug delivery strategies, and the use of the stent as a delivery platform.

A drug-eluting stent (DES) is a peripheral or coronary stent (a scaffold) placed into narrowed, diseased peripheral or coronary arteries that slowly release a drug to block cell proliferation. This prevents fibrosis that, together with clots (thrombus), could otherwise block the stented artery, a process called restenosis. The stent is usually placed within the peripheral or coronary

artery by an Interventional cardiologist or Interventional Radiologist during an angioplasty procedure[1].

Drug-eluting stents in current clinical use were approved by the FDA after clinical trials showed they were statistically superior to bare-metal stents (BMS) for the treatment of native coronary artery narrowings, having lower rates of major adverse cardiac events (MACE) (usually defined as a composite clinical endpoint of death + myocardial infarction + repeat intervention because of restenosis).

When blockages in the arteries of the heart (coronary arteries) develop, individuals may experience symptoms caused by inadequate blood supply to the heart muscle. This typically produces chest pain or pressure and/or shortness of breath. Treatment for this condition (coronary artery disease) will depend on the type of the blockage and its extent. Treatment options include medication, surgery (coronary artery bypass surgery), or catheter-based procedures, which are discussed below[2]. Patients should discuss these options with their physician to determine which may be best for them.

Several types of catheter-based procedures are available. During balloon angioplasty, the physician passes a special balloon catheter into the narrowed segment of the artery and expands the balloon, which thus opens the artery and compresses the blockage against the wall of the artery. More than one third of patients who undergo balloon angioplasty may experience restenosis (renarrowing) of the diseased artery segment within 6 months of the procedure. Stents are very small metal tubes that can be inserted via a balloon catheter into the narrowed segment of the artery[3]. When the balloon is inflated, the stent expands and is embedded into the artery vessel wall, which thus opens the previously narrowed segment of artery. The balloon is then deflated and removed along with the catheter, and the stent is left behind to serve as a metal framework for the artery. Although stented arteries have less chance of renarrowing than arteries opened with a balloon alone, in-stent restenosis can still occur in more than 1 in 5 patients after stent placement.

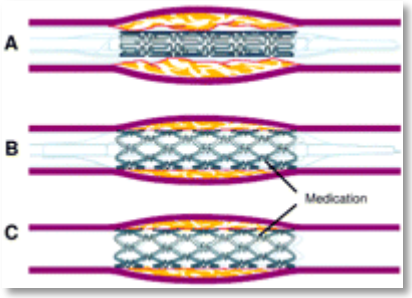

Figure-1. A, The stent is mounted on a balloon catheter and advanced to the diseased, narrowed portion of the heart artery. B, The balloon is inflated and the stent is expanded, which opens the narrowed section of the artery. C, The balloon is deflated and removed; the stent is embedded into the wall of the artery and stays in position. Medication coats drug-eluting stents and reduces the chance of renarrowing, or restenosis, of the blood vessel.

Because restenosis within the stented region of a heart artery is caused by tissue growth, some stents (called drug-eluting stents) have medication on them to inhibit or prevent this tissue growth. Drug-eluting stents are placed in a fashion similar to other stents; however, their use markedly reduces the rate of renarrowing. In fact, about 1 in 10 patients develops renarrowing in the several years after drug-eluting stent implantation, a rate about half of that seen for stents without medication[4].

Because stents expose foreign material to the blood stream, a small risk exists that a blood clot may develop in the stent, a process called stent thrombosis. These blood clots can occur many months and even years after stent implantation and may lead to a heart attack or death. All stents can potentially be affected by stent thrombosis. For this reason, most patients with

stents are instructed to take anticlotting medication, usually a combination of aspirin and clopidogrel or ticlopidine[5]. Each of these medications stops platelets (particles in the blood that help clots to form) from functioning to their full capacity. The precise duration of anticlotting medication depends on the type of stent placed by your doctor and your overall medical condition. If you have been prescribed anticlotting medications, you should not stop them (even for a few days) unless instructed to do so by your doctor.

Concerns about the safety of drug-eluting stents have received much publicity, primarily related to a small increase in the number of blood clots that develop within drug-eluting stents late (more than 1 year) after implantation. In December 2006, the US Food and Drug Administration convened a panel of cardiovascular experts to review drug-eluting stent safety data. The panel concluded that for many patients, such as those with uncomplicated medical histories who undergo elective stenting of simple coronary blockages, drug-eluting stents remain a safe and appropriate therapy[6]. For others, such as those who have suffered an acute heart attack or those with multiple or complicated coronary blockages, current data are inadequate to determine whether drug-eluting stents are better or worse than bare-metal stents or coronary artery bypass surgery. Patients are advised to discuss with their physician which treatment option(s) may be most appropriate for them. In all cases, patients who receive drug-eluting stents are reminded to take their prescribed anticlotting medications without interruption for at least 1 year after stent implantation, unless otherwise instructed by their cardiologist.

Pathophysiology of ISR and mechanism of action of DES to prevent ISR

Three distinct processes are involved in the pathogenesis of ISR as depicted in **Figure 1**. These include: (1) immediate vessel recoil after stretch injury, (2) negative arterial remodeling, and (3) neointimal hyperplasia (Hoffmann et al 1996; Mintz et al 1996; Liu et al 2002; Muhlestein et al 2002). Elastic recoil is the immediate shrinkage of vessel after percutaneous coronary intervention (PCI) due to the elastic properties of arterial wall, which usually occurs within 24 hours after procedure[7, 8]. Negative remodeling is a process of local contraction of arterial wall and narrowing of the lumen at the injured vascular segment. It may be related to the healing process as well as the interaction between endothelial cells and nonlaminar blood flow (Liu et al 1989). Neointimal hyperplasia is the proliferation and migration of smooth muscle cells from the media, possibly circulating cells from bone marrow into the intima, and then encroaches on the vascular lumen (Liu et al 1989). Negative remodeling and neointimal proliferation usually occur weeks to months after PCI (Liu et al 1989). The first two pathological processes were the main causes of restenosis in BA, but were basically eliminated by use of stent. The third mechanism, neointimal hyperplasia, becomes the only major mechanism in the pathogenesis of ISR (Virmani and Farb 1999).

Stent-based drug delivery system

The main processes of ISR, smooth muscle cell activation and replication, occur locally at the site of injury. Therefore, one of the most logical approaches is a stent-based drug delivery system to locally deliver an appropriate concentration of an effective agent to stop this process without systemic toxicity. An effective system would consist of 3 components: (1) a metallic platform,

(2) a drug carrier vehicle that stores a therapeutic agent as well as allows the agent to diffuse into the vascular tissue in a controlled fashion, and (3) an effective therapeutic agent that reduces the neointimal growth induced by stent implantation[9, 10]. The cross-section of a stent strut with typical coating configuration can be seen in **Figure 2**. Therefore, an ideal DES to achieve the greatest clinical efficacy and safety is one that requires an optimization of these three essential parameters.

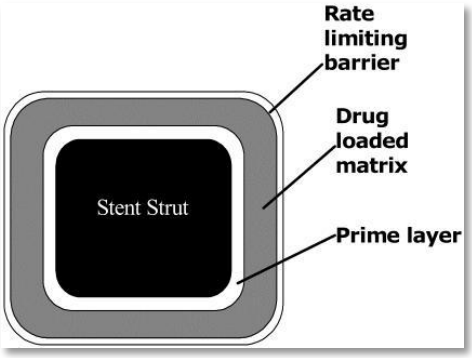

Figure 2: Cross-section of a stent strut with a drug-loaded polymeric coating.

Stent design in relation to even drug distribution to vessel wall

The effect of different stent designs on the drug distribution pattern has been scrutinized in experimental studies and also tested in clinical trials (Hwang et al 2001; Takebayashi et al 2004). Recent experimental data suggest that the stent strut configuration directly determines the pattern and degree of drug delivery achieved by DES (Hwang et al 2001). The simple proximity of stent struts to vascular tissue does not ensure adequate drug delivery and distribution because most nonuniform distribution has been found in the layers of the artery closest to the stent (Hwang et al 2001). After deployment of even highly lipid-soluble and rapidly diffusing agents, homogeneous drug delivery throughout the vessel with uniform concentration at various depths of the vessel wall was not achieved in their study[11]. In the same study, the uniformity of drug distribution was found to be increased with the strut number as well as significantly dependent on the strut pattern of distribution. Therefore, a symmetric expansion of stents with homogeneous distribution of struts is essential for the optimization of drug distribution.The importance of this concept was further verified by a recent clinical study using Sirolimus-eluting stent (SES) (Takebayashi et al 2004). In the latter study, a nonuniform stent strut distribution and a greater gap distance between struts after stent implantation resulted in more neointimal hyperplasia (Takebayashi et al 2004). Although a large number of stent designs have been developed to date, only the multicellular design is currently most commonly used; they can be categorized into “closed cell” and “open cell” configurations (Rogers 2002). A closed cell stent has a uniform cell expansion and constant cell spacing when deployed in a curved vascular segment, which gives more uniform drug distribution (Rogers 2002). An open cell stent has a greater variation in the surface coverage between the inner and outer curvatures in the curved segment, but gives better conformability to curved surface at the expense of less uniform drug distribution (Rogers 2002). The majority of current BMS use a closed cell design. In summary, the optimal stent design for drug delivery should have a large stent surface area, a small cell gap, and minimal strut deformation after deployment while maintaining conformability, radial support, and flexibility to reach the complex coronary lesions[12].

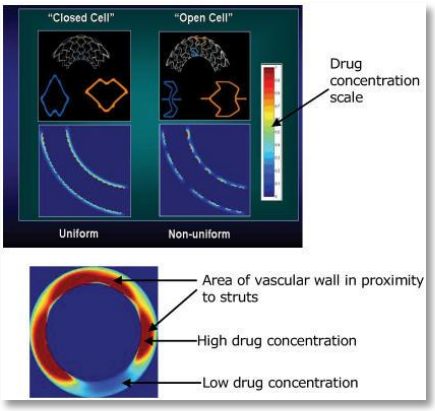

Figure 3: Uniform vsnonuniform drug distribution in closed cell vs open cell stents was shown in the longitudinal sections of the vessel wall after a deployment of a drug-eluting stent. Drug concentration was shown in the color intensity in the column. Upper red-brown...

Coating matrix as a reservoir for drugs and controller of kinetic drug release

Many methods of coating stents with drugs have been developed for DES (Figure 4). Some drugs can be bonded directly to a metal stent (eg, prostacyclin, paclitaxel), but most of the agents must be bonded to a matrix polymer, which acts as a drug reservoir to ensure drug retention during deployment and a uniform distribution on the stent (Sousa et al 2003a). The types, compositions, and designs of the polymers coated on the stent dictate the eluting kinetic of the sustain time release of the drug over a period of weeks or months following the implantation in situ[13, 14]. The coating materials can be categorized as organic vs inorganic, bioerodablevsnonbioerodable, and synthetic vs naturally occurring substances (Sousa et al 2003a). Generally, for long-term application, a nonbioerodable polymer is used in order to prevent triggering an inflammatory process. The most successfully tested DESs to date have been coated with synthetic polymers; poly-n-butyl methacrylate and polyethylene-vinyl acetate with sirolimus and a poly (lactide-co-Σ-caprolactone) copolymer with paclitax-eleluting stents[15]. All naturally occurring organic materials are both bio- and hemo-compatible (Ratner 1993; De Scheerder et al 2000). Fibrin, cellulose, and albumin have been tested in animal models, but only phosphorylcholine is used for clinical purposes. Phosphorylcholine is a naturally occurring phospholipid polymer with less potential to elicit inflammation and to interfere with re-endothelialization of the stent surface (Lewis et al 2002). BiodivYsio® stents are phosphorylcholine-coated stents currently available (Galli et al 2000). Inorganic substances have also been tested for coating on the stent surface to improve electrochemical properties. One example is a stent coated with a nonporous 300 µm ceramic layer containing tacrolimus-loaded nanocavities (Grube et al 2003).

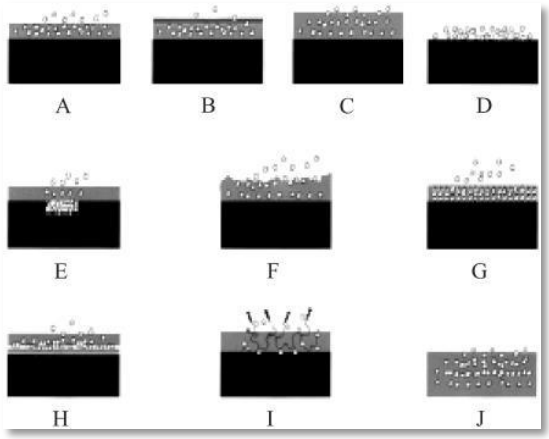

Figure 4: Different types of stent-based drug delivery system: (A) Drug released by diffusion from polymer, (B) Drug released by diffusion through ratelimiting coating, (C) Drug released by swelling of coating, (D) Drug release directly from coating, (E) Drug loaded ...

Therapeutic agents to inhibit neointimal growth

Many agents with antiinflammatory or antiproliferative properties have been incorporated on the stent surface Tables 1 and .2). Many of the agents listed in the tables have more than one mechanism of action. The general mechanism of action for most of these drugs is

to stop cell cycle progression by inhibiting DNA synthesis[16]. Everolimus, sirolimus, tacrolimus (FK-506), ABT-578, interferon, dexamethasone, and cyclosporine all fall into this category. In this group, sirolimus and its derivatives were shown to reduce intimal thickening (Sousa et al 2001; Sousa, Costa, et al 2003).

Table 1
Agents used in drug-eluting stent

Antineoplastics and antiinflammatory immunomodulators	Antiproliferative	Migration inhibitors and ECM modulators	Enhanced healing and re-endothelialization factors
Sirolimus	QP-2, Taxol(paclitaxel)	Batimastat	BCP671
Tacrolimus	Actinomycin	Prolyl hydroxylase inhibitors	VEGF
Everolimus	Methotraxate	Halofunginone	Estradiols
Leflunomide	Angiopeptin	C-proteinase inhibitors	NO donor compounds
M-Prednisolone	Vincristine	Probucol	EPC antibodies
Dexamethasone	Mitomycine		Biorest
Interferon r-1b	Statins		
Mophenolic acid	C-*myc* antisense		

Table 1: Agents used in drug-eluting stent

DIFFERENT TYPES OF STENTS BASED ON GENERATION

1. First-Generation Stents

SES and PES revolutionized rates of restenosis after cardiac procedures. These stents were developed to prevent the proliferation of smooth-muscle cells and other cell types seen with restenosis. The FDA approved SES and PES for use in patients with newly diagnosed, previously untreated single lesions <28 mm to 30 mm in length and a vessel diameter between 2.5 mm and 3.75 mm[17].

Sirolimus is a macrocytic triene antibiotic that has immunosuppressive and antiproliferative properties and elutes slowly over 4 to 6 weeks.1 The efficacy of SES in preventing restenosis was demonstrated in the RAVEL, SIRIUS, and SCANDSTENT trials and the RESEARCH registry.2-8 RAVEL and SIRIUS, which compared SES with BMS, included stented patients with stable or unstable angina who received DAPT for 6 to 9 months[18]. In the trials, there was a significant reduction of in-stent restenosis, late lumen loss, and target lesion revascularization (TLR) over 1 to 5 years. In all trials, there was no difference in rates of death or myocardial infarction (MI).

Paclitaxel, an antineoplastic, works by disrupting the function of the microtubules responsible for proper chromosome segregation during cell division, and it is released bimodally over a 2-week period.[19] The efficacy of PES was demonstrated in the TAXUS II and TAXUS IV trials, which examined patients with low-risk lesions or previously untreated coronary stenosis who randomly received BMS or PES with either a slow or a moderate drug-release rate. All trials resulted in reduction of in-stent restenosis and TLR.10-12 Furthermore, TAXUS IV demonstrated

that these benefits were maintained in subgroups, including patients with vessels <2.5 mm in diameter, those with lesions >20 mm in length, and those with renal insufficiency or diabetes.13 Pooled and long-term analysis also revealed a reduction in cardiovascular (CV) events.14,15 The newest member of the PES series is the TAXUS Liberté, which has thinner struts to improve deliverability and was shown to be noninferior to its prototype in the TAXUS ATLAS trial[20].

PES and SES were compared in several clinical trials, most of which concluded that SES were associated with lower rates of clinical restenosis and late lumen loss. The superiority of SES may be due to differences in mechanism of action, timing of drug delivery, and cellular inflammatory response for SES and PES at sites of overlapping stents.

Second-Generation Stents

The newer stents, EES and ZES, are thinner and more flexible and have a cobalt-chromium alloy platform, which makes them more deliverable than the first-generation stents. These stents may also be more biocompatible, thereby generating less inflammatory response and faster vessel endothelialization[21].

Everolimus, a sirolimus derivative, is a semisynthetic, lipophilic, highly absorbable macrolide immunosuppressant.25 Everolimus elutes over time, with 80% absorbed within the first month and the remainder eluting over a 4-month period. EES demonstrated efficacy over BMS in the SPIRIT FIRST trial, with significantly lower in-stent late lumen loss at 6 months. EES' superior performance relative to PES was further shown in a meta-analysis of four trials in which EES reduced the risk of stent thrombosis, MI, ischemic TLR, and death. In the SPIRIT II–IV trials, EES and PES were compared in patients with simple and complex coronary disease[22]. EES use resulted in significantly lower rates of in-stent late loss and target-lesion failure (defined by cardiac death, target-vessel MI, ischemic TLR) up to 2 years later.28-33 Although no randomized trials have compared EES and SES, the X-SEARCH registry was used to evaluate the efficacy and safety of EES in higher-risk patients. EES were compared in three historical groups of patients who received BMS, SES, or PES. At 6 months, EES had a significantly lower rate of TLR, compared with BMS, and rates comparable to those with SES and PES[23, 24].

Zotarolimus, also a sirolimus derivative, is a lipophilic immunosuppressant. The polymer used in ZES mimics the cell membrane's phospholipid phosphorylcholine. Ninety-five percent of zotarolimus elutes within the first 2 weeks. The efficacy of ZES has been examined in the ENDEAVOR trials. In ENDEAVOR I and II, which compared ZES with BMS, TLR was lower with ZES at up to 2 years.[25,26] In ENDEAVOR III and IV, which compared ZES with SES and PES, respectively, angiographic in-segment late lumen loss—a surrogate for restenosis—was higher in the ZES group versus the SES group.38,39 Compared with PES, however, ZES was noninferior for the primary endpoint of target-vessel failure.38,39 The SORT-OUT III trial showed similar results in the primary composite endpoint of cardiac death, MI, and TLR, which occurred significantly more often with ZES than with SES.40 The ZEST trial, which compared ZES, SES, and PES, found no difference in the primary composite endpoint of death, MI, and TLR.

In a recent trial assessing EES and ZES in complex clinical or lesion characteristics (renal insufficiency, low ejection fraction, recent acute MI, multiple or long bifurcations, bypass grafts, in-stent restenosis, unprotected left main artery, thrombus, or total occlusion), there was no difference in the primary endpoint of target-vessel failure.

Antiplatelet Therapy with Stents

Coronary rethrombosis and coronary restenosis are sequelae of stent placement. Coronary rethrombosis is defined as reocclusion of coronary vessels by thrombin formation, and coronary restenosis is reocclusion of coronary vessels and smooth-muscle endothelial overgrowth.[27]Thesesequelae can lead to devastating events such as MI and death. DES are associated with a reduced risk of restenosis but an increased risk of rethrombosis, specifically with early discontinuation of DAPT.

Predictors of later DES thrombosis have been identified, including patient and angiographic characteristics. Patient characteristics consist of older age, diabetes mellitus, low cardiac ejection fraction, renal failure, and ACS. In addition, early discontinuation of antiplatelet medications has been identified as a risk factor for stent thrombosis. Angiographic characteristics such as long or overlapping stents, stent placement in small vessels, bifurcation lesions, and suboptimal stent results also increase the risk of DES thrombosis[28].

The American College of Clinical Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Intervention (ACCF/AHA/SCAI) guideline for PCI, updated in 2011, includes new recommendations for the prevention of stent thrombosis.[29] The guideline stresses that PCI with coronary stenting (BMS or DES) should not be performed if the patient is unlikely to tolerate and comply with DAPT for the appropriate treatment duration based on the type of stent implanted.

COMMERCIALLY AVAILABLE DES

The sirolimus-eluting Cypher™ stent (Cordis Corp, a Johnson and Johnson Company, Miami, FL, USA) was approved by FDA in April 2003. It is coated with a layer of nonerodable polymer, of 5 µm–10 µm thickness, which is incorporated with sirolimus (140 µgsirolimus/cm2 of stent surface area). An additional topcoat is placed on it as a diffusion barrier, which provides the vehicle for controlled release of the drug. It is designed as such that approximately 80% of the total dose of the agent is released in 4 weeks and the remainder over the course of the next 2 weeks (Wong and Chan 2004). The second commercially available DES is the Taxus™ stent (Boston Scientific, Natrick, MA, USA), which has a proprietary platform, the Express™ stent, and is coated with a proprietary polymer (Translute™) loaded with 1 µg of paclitaxel/mm2 of stent surface area. Although there are three drug-release formulations (slow, moderate, and fast), only moderate- and slow-release formulations have been tested in clinical trials (Sahatjian 2003; Waugh and Wagstaff 2004). The moderate-release (MR) form of Taxus stent allows for an initial bolus release over the first 48 hours after stenting followed by a low-level release over at least the next 10 days. In the initial 10 days of drug release, the slow-release (SR) formulation of Taxus stent has a drug release concentration of 8–10 times lower than that of the MR formulation. Only SR formulation is used in FDA approved Taxus stents. (Sahatjian 2003; Waugh and Wagstaff 2004).

CURRENT ISSUES OF DES

Expanded indications

Although DES was proved to be a safe and effective method in the treatment of coronary artery stenosis by both randomized clinical trials and real world practice, its expanded indications in complex and high-risk lesions for restenosis such as totally occluded lesions, left main lesions, bifurcation lesions, ostial lesions, small and long lesions, saphenous vein graft lesion, ISR, and diabetes mellitus are still under evaluation with ongoing trials. The results of

clinical trials for some expanded indications are now available.

Issue of stent-based delivery: incomplete stent apposition and uneven stent strut distribution

Incomplete stent apposition (ISA), defined as one or more stent struts not in contact with vascular wall on IVUS at any point in time after stent implantation, was found in 21% of the SES arm in RAVEL vs 4% in the BMS arm at 6-month follow-up (Serruys et al 2002). It is possible that this is due to either an initial incomplete deployment of stent during implantation or positive remodeling of vessel wall but other mechanisms like plaque regression, cell necrosis, apoptosis, and allergic reaction to sirolimus have been postulated (Lemos et al 2003; Takebayashi et al 2004). Uneven stent strut distribution and incomplete wall apposition has been considered to be the causes of ISR after the DES implantation in two clinical studies (Lemos et al 2003; Takebayashi et al 2004).

Economic burden

One of the thorniest issues regarding DES is their cost and reimbursement. In the USA, a BMS costs approximately $900–$1200 each while a DES costs approximately $3065–$3195. However, in the cost-effective analysis of SIRIUS trial, the difference of cost between the 2 groups were only about US $300 at 1 year, despite an initial $3000 difference after hospitalization (Cohen et al 2003). The advent of more varieties of DES in near future will minimize the cost issue and make DES available to all patients.

Role of the Pharmacist

FDA advisories stress the importance of carrying out 12 months of DAPT after DES placement and advise educating the patient and health care providers about the hazards of premature discontinuation. The role of the pharmacist is to encourage patients to continue therapy through education and to promote the use of adherence programs provided through the pharmacy.

DES Systems with Bioabsorbable Polymers

Since durable, thick polymers of first-generation DES seem to have a central role in perpetuating local vascular inflammatory reaction and potentially inducing the occurrence of late and very late stent thrombosis, the concept of a polymer that carries and controls the drug release during an proper period of time and after that erodes and vanishes from the vascular surface seems to be very attractive. Most of the systems presented in this section utilize poly-l-lactic acid (PLLA) and poly-d,l-lactide (PDLLA), which are progressively erode by shortened as ester bonds and ultimately will degrade into lactic acid[30].

MAIN DES SYSTEMS WITH BIOABSORBABLE POLYMERS

BioMatrix (Biosensors Inc)

The BioMatrix (Biosensors Inc, Newport Beach, Calif) stent is a novel DES that incorporates the S-Stent platform, a thin, stainless steel, laser-cut, tubular stent with 16.3% to 18.4% metal surface area. The antiproliferative drug is biolimus A9, a highly lipophilic, semisynthetic sirolimus analogue with an alkoxy-alkyl group replacing hydrogen at position 42-O. At a cellular level, biolimus A9 forms a complex with intracellular FKBP-12, which binds to the mammalian target of rapamycin and reversibly inhibits cell-cycle transition of proliferating smooth muscle cells with a similar potency to sirolimus. On the basis of in vivo studies, the biodegradable polymer fully converted to lactic acid at 6 to 9 months (data on file at Biosensors).

Cardiomind 0.014-Inch Sparrow (CardioMind, Inc)

The Sparrow Coronary Stent System (CardioMind, Inc, Sunnyvale, Calif) is a 0.014-inch guide wire–based stent delivery platform combining a limus drug in a biodegradable

polymer matrix on the CardioMindnitinol stent platform with a novel release mechanism that uses a principle of electrochemical dissolution for stent release.

ELIXIR-DES Program (Elixir Medical Corporation)

Elixir Medical Corporation is currently working with 2 pharmaceutical agents, Novolimus, a metabolite of sirolimus, and Myolimus, a sirolimusanalog. Both drugs belong to the family of macrocyclic lactones with immunosuppressive and antiproliferative properties and have a similar mechanism of action to other macrocyclic lactones such as rapamycin. The Elixir Medical Drug-Eluting Coronary Stent Systems (Elixir Medical Corp, Sunnyvale, Calif) are designed to optimize safety and efficacy through the combination of a cobalt chromium stent platform, a low polymer loading with controlled release and a low pharmacological drug dose.

CONCLUSION

After several years involved in the task of "bringing to life" novel devices to treat coronary disease, the recent introduction of DES in PCI is a major innovative advancement in interventional cardiology. DES dramatically reduces the ISR rate in all subgroups of patients in both randomized clinical trials and real-world practice. Continuing improvement in drug-delivery stent technologies and gradual reduction in cost would make DES an effective mainstay of therapy for coronary artery disease.

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