Current status and future prospects of drug eluting stents for restenosis

MAULIK J. PATEL*
SANJAY S. PATEL
NIDHI S. PATEL
NATVARLAL M. PATEL

Shri B. M. Shah College of Pharmaceutical Education and Research, Modasa-383315 Gujarat, India

Drug-eluting stents (DESs) prevail in the treatment of carotid artery diseases in the interventional cardiology world owing to their efficacy for significant reduction of restenosis. A current successful DES requires a polymer coating for drug delivery. Clinical trials examining several pharmaceutical agents have demonstrated marked reduction in restenosis following stenting. The development of DES is one of the major revolutions in the field of interventional cardiology. The ideal drug to prevent restenosis must have an anti-proliferative and anti-migratory effect on smooth muscle cells but, on the other hand, it must also enhance re-endothelialization in order to prevent late thrombosis. Additionally, it should effectively inhibit the anti-inflammatory response after balloon induced arterial injury. Although DES have significantly reduced the angiographic restenosis rate and have improved clinical outcomes, late thrombosis and restenosis remain an important subject of ongoing research.

Keywords: drug eluting stent, restenosis, biodegradable polymer

Drug-eluting stents (DES) are coated stents capable of releasing single or multiple bioactive agents into the bloodstream and surrounding tissues. Stents represent a major advance in the treatment of obstructive coronary artery disease since the advent of balloon angioplasty. Angioplasties have doubled in Europe from 1992–1996. Much research has been devoted to the pathophysiology and treatment of in-stent restenosis.

Disease-induced narrowing in the fluid-carrying vessels of the human body can occur in a wide variety of circumstances. For example, blockages in the vascular system can deprive the downstream tissue of oxygenated blood, constrictions of the urinary tract can lead to pain and loss of renal function, and biliary duct blockages can lead to pathologic jaundice. In the past, open surgical approaches were used to solve these problems, but more recently, stents have been used; a stent may be defined as a device

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* Correspondence; e-mail: maulik2121@gmail.com

that is intended to keep a biological passageway open. Most often stents take the form of cylindrically shaped devices that press out against the vessel or duct wall thereby restoring patency (patency of a vessel or duct refers to it being open or unobstructed). Since the early 1990s, stents have revolutionized the treatment of vascular diseases; they were first reported for use in restoring patency in the coronary artery. Since then, their use has accelerated to the degree that 1.5 million cardiovascular stenting procedures are performed in the United States annually (1).

However, three types of post-stent narrowing of the vessel may occur:

(i) The compressive force created by the vessel may cause elastic recoil of the stent and an associated immediate narrowing of the lumen.

(ii) Injury caused by stent deployment may initiate intimal hyperplasia (IH), whereby smooth muscle cells in the vessel wall proliferate into the lumen (the inner part of the vessel) causing a process of re-stenosis to occur over time.

(iii) Remodeling of the vessel wall may occur as the stiffness of the vessel wall changes in response to the stresses generated in the tissue and the vessel narrows, termed »negative« remodeling.

Renarrowing of a stented vessel is termed in-stent restenosis (ISR) and it involves the formation of IH though a complex cascade of post-stenting cellular events (2).

Restenosis rates, or binary restenosis rates, are defined by the number of stented vessels that have over 50 % vessel lumen stenosis at follow-up post-stenting; they have been reported for many different stent designs from the results of clinical trials. Based on 20–50 % restenosis rates in some stent designs, drug-eluting stents were developed in the early 2000s.

Drug-eluting stents have shown superior performance in prevention of in-stent restenosis; one of the key clinical trials showed a reduction from 26.6 % for the bare-metal stents to 7.9 % for the drug-eluting stents. A stent should be sufficiently flexible in bending during expansion to not unduly straighten curved vessels; it must have sufficient scaffolding properties (*i.e.*, there should be minimal prolapse or »draping« of the inner lumen between the struts of the expanded stent, and stenotic material should not be so highly stressed to make a part of it break off); the amount of shearing of the metal stent over the vessel wall during expansion should be minimized as such shearing could denude the vessel wall of its endothelial cell lining; the stent should not foreshorten during expansion (*i.e.*, the degree of longitudinal contraction during expansion should be as small as possible).

Drug-eluting stents deliver potentially high doses of drugs locally for variable time periods in the area of stent implantation directed to the potential restenosis site. While this is currently achievable, optimal pharmacological therapy is still evolving. Neointima proliferation, the prime cause of restenosis in stent error, is the result of a local injury response modulated by platelet and fibrinolytic effects, inflammation as well vascular (endothelial) healing. Choosing the optimal drug(s) and doses for stent delivery will require testing to optimally prevent proliferation while enhancing healing. The time course of drug delivery is also important. Finally, potential complications must be evaluated.

WHY DRUG-ELUTING STENTS?

In 1991, stent use was still facing skepticism because of an unacceptably high (20 to 25 %) incidence of thrombotic complications (3). Systemic anticoagulation proved disappointing in reducing the catastrophic consequences of stent thrombosis, such as myocardial infarction and sudden death. Consequently, antithrombotic stent coatings were developed to decrease the inherent thrombogenicity of coronary metallic stents. Some heparin-coated stents became available for clinical use. Heparin-coated stents differ from drug-eluting stents because the medication is covalently bonded to the device and hence may remain attached long after deployment. These stents represented the first step toward loading medications onto stents. Fortunately, the incidence of subacute stent thrombosis has dropped significantly to 0.5 % because of high-pressure stent deployment and the use of antiplatelet agents (4).

STEPS INVOLVED IN MANUFACTURING DRUG-ELUTING STENTS

In clinical practice, the operator must decide which stent is most appropriate for the patient, and even more importantly, for the lesion that is going to be treated. General characteristics pertaining to the »ideal« stent are listed in the following:

- ➢ flexible,
- ➢ trackable,
- ➢ low unconstrained profile,
- ➢ radio-opaque,
- ➢ thromboresistant,
- ➢ biocompatible,
- ➢ reliably expandable,
- ➢ high radial strength,
- ➢ circumferential coverage,
- ➢ low surface area,
- ➢ hydrodynamic compatible.

Stents can be wound coils, woven mesh designs, or laser-cut designs. Most stents available today are laser-cut stents and the closed-cell types are slotted tubes whereby the stent geometry is machined from a full cylinder so that no welds exist in the structure; examples include the NIR, Be Stent, and inflow stent designs.

FABRICATION TECHNIQUES

The choice of fabrication method mainly depends on the raw material form used. Wires can be formed into stents in various ways using conventional wire-forming techniques, such as coiling, braiding or knitting. The simplest shape for a wire stent is a coil. All coil stents marketed today are made of nitinol and are self-expanding. Welding at

specific locations after wire forming produces closed-cell wire stents or increases longitudinal stability.

The vast majority of coronary stents, and probably the majority of peripheral vascular stents, are produced by laser cutting from tubing. Balloon-expandable stents are cut in the crimped or near-crimped condition, and only require post-cutting deburring and surface treatment, typically electro-polishing.

Step I

The carrier stent. – Endovascular stents were initially designed as scaffolding structures, not medication-delivery devices. Consequently, stent design has been altered to afford more flexibility, greater radial strength, and minimal metallic coverage. Efforts are now directed at coating a stent with a sufficient amount of medication that can be delivered uniformly to the underlying tissue. Uniform drug distribution in human, diseased coronary arteries is unrealistic, however. Besides stent design, other factors govern drug diffusion, such as vessel wall morphology, drug physicochemical characteristics, and the multifaceted milieu of the underlying atherosclerotic plaque.

Compared with current stents, the ideal drug-delivery stent might have a much larger surface area, minimal gaps between cells, and minimal strut deformation after deployment.

Step II

The coating matrix is a double edged sword. – There are several approaches to coating stents with medications. Some drugs can be loaded directly onto metallic surfaces (*e.g.*, prostacyclin, paclitaxel), but a coating matrix that contains the medication is required for most biological agents (Fig. 1). The coating ensures drug retention during deployment and modulates drug-elution kinetics.

In theory, sustained release of anti-restenotic drugs for at least 3 weeks after deployment is required to prevent smooth muscle cell migration and proliferation. Drugs may be held by covalent bonds (*e.g.*, C-C bonds, sulfur bridges) or non-covalent bonds (*e.g.*, ionic, hydrogen bonds) (5). The blended matrix may then be attached to the stent surface by dipping or spraying the stent.

Drug is released by particle dissolution or diffusion when non-bioerodable matrices are used, or during polymer breakdown when incorporated (absorbed) into a biodegradable matrix. The coating material should act as a biologically inert barrier. Selection of a non-inflammatory, inert coating matrix has been a major obstacle to the development of drug-eluting stents. Coating materials must maintain their physicochemical characteristics after sterilization and after stent expansion. These substances may be categorized as organic, inorganic, bioerodable, non-bioerodable, synthetic, or naturally occurring substances (6).

Synthetic polymers. – To date, the most successfully tested drug-eluting stents have been coated with synthetic polymers: poly-*n*-butyl methacrylate and polyethylene–vinyl acetate with sirolimus, and a poly(lactide-co-caprolactone) copolymer with paclitaxel eluting platforms (7).
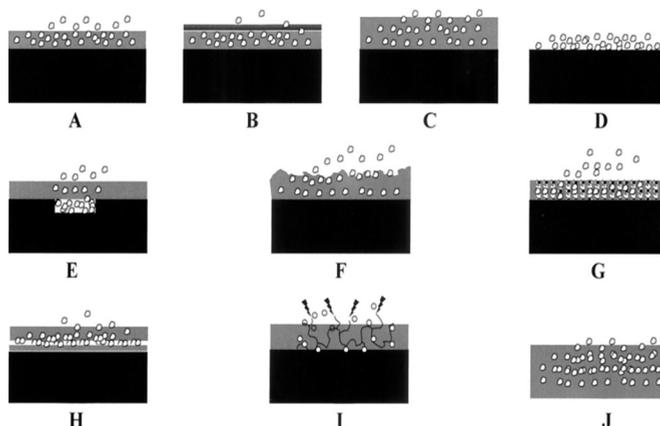
Fig. 1. Schematic representation of different modalities of drug-eluting stent platforms (black represents stent strut; gray, coating). A) drug-polymer blend, release by diffusion, B) drug diffusion through additional polymer coating, C) drug release by coating swelling, D) non-polymer-based drug release, E) drug loaded in stent reservoir, F) drug release by coating erosion, G) drug loaded in nanoporous coating reservoirs, H) drug loaded between coatings (coating sandwich), I) polymer-drug conjugate cleaved by hydrolysis or enzymatic action, J) bioerodable polymeric stent.

Biological materials. – The surfaces of a vascular prosthesis must be both bio- and hemo-compatible (8). Fibrin, cellulose, and albumin, all naturally occurring, have been tested to improve the quality of stent surfaces, with promising results from animal studies.

Inorganic coatings. – Inorganic substances have been placed on stent surfaces to improve their electromechanical properties. In addition, other ongoing studies involve stents designed with a deep reservoir for drug loading coated with a thin layer of pyrolytic carbon (Carbofilm).

Step III

The biological agent. – The ideal anti-restenotic agent for local delivery should have potent anti-proliferative effects and yet preserve vascular healing. Such a compound should contain hydrophobic elements to ensure high local concentrations, as well as hydrophilic properties to allow homogeneous drug diffusion. Other factors such as molecular mass, charge, and degree of protein binding may also affect drug kinetics and ultimately influence the biological success (9).

Anti-cancer and anti-transplant rejection agents are now being considered in the fight against restenosis drugs that interfere earlier in the cell cycle (G1 phase); they are generally considered cytostatic and potentially elicit less cellular necrosis and inflammation compared to agents that affect the cell cycle at a later stage (beyond the S phase) (10). On the basis of the mechanism of action of the biological compound and its target in the restenotic process, drug-eluting stents may be generally classified as immunosuppressive, anti-proliferative, anti-inflammatory, anti-thrombotic, and prohealing.

DESIGN NECESSITIES OF STENTS

Intravascular stents, whether expanded using a balloon or self-expanding, are delivered *via* femoral or brachial arteries through the tortuous vessels of the cardiovascular system. To minimize in-stent restenosis, stents must fulfil the following expanded list of design requirements:

(i) High radial strength: Required radial support/structural strength to prevent vessel recoil and hence lumen loss post-stenting.

(ii) A measure of elastic recoil: It may be defined by (Rload-Runload)/Rload, where R represents the radius of the stented vessel for full balloon expansion (load) and after deflation of the balloon (unload).

(iii) Good flexibility: The crimped stent on the delivery catheter must be flexible so that it can be delivered to the deployment site.

(iv) Low stent profile: The crimped stent on the delivery catheter should have a low profile to prevent excessive flow disturbances during delivery and once deployed.

(v) Good trackability: Trackability is a measure of the ability of a stent deployment catheter to follow the tortuous path to its ultimate destination. Trackability depends on shaft flexibility, which should be high, friction between the stent and its surrounding environment, which should be low to prevent damage to the vessel wall and hinder the movement of the catheter, axial stiffness, which should be high so as to reduce axial deformation of the catheter.

(vi) Minimal foreshortening: The measure of foreshortening may be defined by (Lload)/L, where L represents the length of the stent before deployment, and Lload, the length of the stent after balloon inflation.

(vii) Minimal elastic longitudinal recoil: Foreshortening and longitudinal recoil may also cause undesirable shearing along arterial walls, which can cause injury in the form of denudation of the endothelial cells from the lumen of the vessel during stent expansion.

(viii) Optimum scaffolding: A stent should provide optimum vessel coverage to ensure that the vessel tissue does not prolapse between the stent struts; however, a low artery-stent contact surface area should also be maintained, because the foreign material of the stent can initiate an aggressive thrombotic response.

(ix) Stent material requirements:

➢ Radiopacity: Stent materials need to be radiopaque to enable delivery, precise positioning, and evaluation of stents in follow-up under the guidance of fluoroscopic imaging.

➢ Biocompatible: Stent materials must be biocompatible so as not to elicit an adverse reaction from the body.

➢ Corrosion-resistant: Stent materials are chosen which prevent corrosion by the development of a passive oxide layer.

➢ Good fatigue properties: Cyclic stresses because of blood flow can cause fatigue failure in stents (11).

All of these design requirements can be achieved by optimizing the following parameters:

(i) material selection,

(ii) strut dimensions and cross-section,

(iii) number of circumferential and axial repeating units, and their geometry,

(iv) the manufacturing process used to produce stents.

STENT DESIGN

Geometry of stent platforms

The subsequent evolution of stent design yielded the development of a rich variety of stent geometries, which can be classified into five main high-level categories: coil, helical spiral, woven, individual rings or sequential rings (12).

Coil. – Most common in non-vascular applications, as the coil design allows for retrievability after implantation. These designs are extremely flexible, but their strength is limited and their low expansion ratio results in high profile devices (13).

Helical spiral. – These designs are generally promoted for their flexibility. With no or minimal internal connection points, they are very flexible, but lack longitudinal support. As such, they can be subject to elongation or compression during delivery and deployment and, consequently, irregular cell size formation.

Woven. – This category includes a variety of designs constructed from one or more strands of wire. Braided designs are often used for self-expanding structures.

Individual rings. – Single »Z« shaped rings are commonly used to support grafts or similar prostheses; they can be individually sutured or otherwise attached to the graft material during manufacture. These structures are not typically used alone as vascular stents.

*Sequential ring*s. – This category describes stents comprising a series of expandable Z-shaped structural elements (known as »struts«) joined by connecting elements (known as »bridges«, »hinges«, or »nodes«).

Closed cell. – These U-, V-, S-, or N-shaped elements plastically deform during bending, allowing adjacent structural members to separate or nest together, to more easily accommodate changes in shape. The primary advantages of closed-cell designs are optimal scaffolding and a uniform surface, regardless of the degree of bending. However, these advantages result in a structure that is typically less flexible than a similar open--cell design.

Open cell. – This category describes construction wherein some or all the internal inflection points of the structural members are not connected by bridging elements. This allows periodic peak-to-peak connections, peak-to-valley connections, and mid-strut to

mid-strut connections, as well as innumerable hybrid combinations. In open-cell designs, the unconnected structural elements contribute to longitudinal flexibility. Periodically connected peak-to-peak designs are common among self-expanding stents, such as the SMART stent, as well as balloon-expandable stents, such as the AVE S7.

Consequently, structures with this type of peak-to-valley connection are generally not so strong as similar structures with peak-to-peak connections. While this peak-to--peak and peak-to-valley connections are the most common, there are also examples of other variations, such as the BeStent, which feature mid-strut to mid-strut connectors.

MATERIALS FOR STENT CONSTRUCTION

Stent materials clearly need to be biologically inert and radiopaque to enable visualization of stent deployment. All stent materials also need to be corrosion-resistant to withstand the highly corrosive environment of the body. The material chosen for a stent depends on the expansion mechanism of the stent, since self-expanding stents must be able to recover considerable elastic deformation and balloon-expanding stents need to deform plastically during deployment. Nickel-titanium alloy and nitinol are the most commonly used material for self-expanding examples RADIUS (Scimed, Singapore) stent and the Medtronic AneuRx AAA Stent Graft (Medtronic, USA). Other materials that have been used in self-expanding stents include a platinum core with a cobalt alloy as the outer layer, which has been used for the mesh of the Wallstent (Boston Scientific, USA).

The most widely used material for balloon-expandable stents is 316L stainless steel, a low carbon (0.03 % maximum) steel that has a high chromium content (17–20 %) and molybdenum (2–4 %) to prevent pitting corrosion in saline solutions. Stents made of 316L stainless steel include the first coronary stent (14). Tantalum Crossflex stent (Cordis Corporation, USA) is a highly radiopaque material, but it has not been used extensively because it is very brittle and therefore more prone to fracture than stainless steel (15). Cobalt chromium has been used for stents in recent years, including the Multilink Vision (Guidant, USA) and Driver stents (Medtronic Vascular, USA), to enable stents with thinner struts to be designed, because cobalt chromium alloys have higher strength than stainless steel.

POLYMERIC POSSIBILITIES

Materials for polymer stents include biodegradable stents coupled with polymeric endoluminal paving, and shape-memory polymers. Silicone was the first organic material chosen for stenting. However, silicone has poor biodurability, tensile and coil strength, and inner to outer diameter ratio (16).

Pure plastic biliary stents using polyethylene or polyurethane have also been used in patients. However, polyethylene induces sludge in 20-30 % of patients, encourages protein adherence and biofilm formation, and entraps bile crystals and food particles. In

contrast, polyurethane has good tensile and coil strength, and good biodurability, but it is also one of the most reactive materials available (17).

Biodegradable and bioabsorbable polymers. – Biodegradable and bioabsorbable stents are also viable materials for stenting. Though biodegradation, bioabsorption, and bioerosion are often used incorrectly as synonyms, they have different definitions. In biodegradation, a biological agent like an enzyme or a microbe is the dominant component in the degradation process. Biodegradable implants are usually useful for short-term or temporary applications. Bioresorption and bioabsorption imply that the degradation products are removed by cellular activity, such as phagocytosis, in a biological environment. In contrast, a bioerodible polymer is a water-insoluble polymer that has been converted under physiological conditions into water-soluble materials. This occurs regardless of the physical mechanism involved in the erosion process. Because of a stent's temporary structural support to damaged blood vessels, biodegradable polymers can be viewed as a biocompatible, yet easily disposable material, perfect for drug delivery systems. Some biodegradable polymers, such as polyesters, polyorthoesters, and polyanhydrides, may be able to modulate the local delivery of drugs and also degrade »safely« *via* hydrolytic and other mechanisms. Biodegradable drug delivery systems require steady degradation, permeability, and moderate tensile strength.

Also, anticoagulants and fibrinolytic agents can be bound directly to collagen, which aids in its capacity for drug delivery. Some factors that accelerate polymer degradation include providing the product with a more hydrophilic backbone, more hydrophilic endgroups, less crystallinity, more porosity, and smaller overall size. The most common chemical functional groups used are esters, anhydrides, orthoesters, and amides.

One concern in using biodegradable stents is the unevenness of the material remaining after the degradation process. Various cells in the body are more likely to bind to uneven surfaces and induce complications. One solution to this dilemma is to provide a smooth surface by using polymeric endoluminal paving. In this process, biocompatible polymers are applied to the surface of an organ or vessel. In »solid« or »structural paving,« tin tubes or sheets of biodegradable polymers are transported intraluminally or intravascularly using a catheter, positioned at the deployment site, and locally remolded with catheter-based thermoforming. »Gel paving« uses hydrogels which swell in the presence of water, but eventually form adherent soft structural walls that develop effective drug delivery reservoirs. In liquid paving, flowable polymeric, macromeric, or pre--polymeric solutions are applied to the underlying tissue surface.

Shape memory polymers. – Once the polymer is synthesized, it may be heated or cooled into myriad shapes. Upon introducing a suitable stimulus, the polymer will undergo transition from its temporary state to a memorized, permanent shape. Most of these polymers are created from suitable segments, primarily determined by screening the qualities of existing aliphatic polyesters, especially poly(etherester), as well as L,L-dilactide, diglycolide, and *p*-dioxanone. Toxicity of the shape-memory polymer system was measured using the chorioallantoic membrane test (CAM test). In this procedure, a sterilized polymer film was incubated for two days in direct contact with the chorioallantoic membrane of a fertilized chicken egg. Then the blood vessels on and around the film were examined. In the first tests performed, biodegradable multiblock polymers showed no influence on blood vessel growth and did not damage the underlying tissue (16).

DRUG DELIVERY METHODS

How may drugs can be delivered in the context of stent implantation? There are three basic routes. First, the drug may be absorbed into a suitable stent material itself, which is intended to act like a sponge. Release of the drug is dependent upon diffusion down a concentration gradient, or upon biodegradation of the stent material. Second, the drug may be chemically bonded onto the surface of stent struts and released after further chemical or biological action of the surrounding milieu or tissue. A combination of this and the above approach may be attempted with a coating, for example a polymer with the necessary tertiary structure, which may be used as a depot for the drug to be held and released, the characteristics of uptake and release being controllable by the composition of the coating 'elution' of the drug from the coating. Third, stent implantation and drug delivery can be treated as separate procedures. The three methods may be combined. In this review, we will sub-divide stent-related local drug delivery into these three categories.

The coating-based release systems can be subdivided into three groups:

➢ diffusion-controlled release,
➢ swelling-controlled release,
➢ biodegradable systems.

Diffusion-controlled release systems

In the diffusion-controlled systems the drug is dissolved or dispersed in a matrix (Fig. 1). When it comes in contact with biological environment, the drug will diffuse out of the carrier coating. Regarding the release profile, two different types of release systems can be differentiated. Matrix systems (Fig. 1, left) have a release rate that decreases over time. But they are often continuous, of the so called zero-order release profile.

Reservoir systems (Fig. 1, right) have a fairly stable diffusion rate. They are built as a core that contains the concentrated agent within a polymer matrix and a shell, and the shell is made of a rate controlling material. The diffusion is driven by the concentration gradient between the core and the outside of the shell or barrier coating.

Swelling-controlled release systems

Another option for drug release is the use of swelling-controlled materials. The material with the drug is compact in the dry state and swells in contact with liquids. Caused by the swelling and often combined with a diffusion process, the incorporated drug is released. The matrix and reservoir systems can be differentiated. Most of the materials used in swelling-controlled release systems are based on hydro-gels. If there is a change of pH, temperature, or ionic strength within the system, then it can either shrink or swell.

Biodegradable release systems

Caused by the biological degradation of the carrier material, the drug releases out of the matrix. Depending on the type and mesh size of the material, diffusion plays a

role too. Corresponding to the type of degradation, the systems are differentiated in bulk and surface degradable systems. Surface degradable systems are favorable for drug delivery systems in blood vessels because the risk of fragment formation and therefore the risk of thrombosis caused by these fragments are minimized.

DRUG DELIVERY APPROACHES

Quality drug carriers can be made with lipids and polymers.

Lipids and liposomes

Some lipids are amphipathic molecules, for example, fatty acids, and phospholipids. Lipids have a dual structure that contains a hydrophilic and a hydrophobic part. They are soluble in organic solvents and form clusters in aqueous solutions. Monolayer, micelles, and liposomes are the favored forms in aqueous solutions.

Liposomes are spherical lipid clusters consisting of one or more lipid bilayers enclosing one or more aqueous compartments. They can mimic several properties of cell membranes, for example, response to osmotic forces, have a permeability barrier, and others. Liposomes are suitable as environmentally responsive systems for drug delivery. Several chemical and physical triggers can stimulate drug release, such as light, electromagnetic field, pH, temperature, polyelectrolytes, *etc.*

Polymers

Many polymers are known to have the potential for drug delivery coatings. Whether a polymer is degradable or not depends on some chemical characteristics such as molecular mass, hydrophobicity, *etc*. In reality, everything degrades, but the question is how fast it degrades. For drug delivery applications, degradation on the human time scale is important. Depending on the implantation site, more biocompatibility aspects have to be considered for these polymers. Other potential disadvantages of polymeric coatings are difficulties with the mechanical behavior after sterilization and expansion if the implant undergoes high plastic deformation.

Hydrogels

Some materials, when placed in water, are able to swell very fast and retain aqueous fluid up to the multiple of their own mass. These hydrogels are usually made of hydrophilic polymer molecules cross-linked by chemical bonds or other cohesion forces such as ionic interaction, hydrogen bonding, or hydrophobic interaction. Owing to their unique bulk and surface properties, they show good biocompatibility and are favorable for several drug delivery applications. They have no interfacial tension with the surrounding biological fluids and tissue, which minimize the driving force of protein adsorption and cell adhesion. Furthermore, hydrogels simulate hydrodynamic properties of natural biological gels, cells, and tissue in many ways.

SELECTION OF DRUGS FOR STENTS

The drugs that may be useful in preventing ISR fall into four major categories: anti--neoplastics, immunosupressives, migration inhibitors, and enhanced healing factors. ISR is primarily due to natural healing mechanisms, including endothelial cell migration and extracellular matrix formation, collectively known as intimal hyperplasia. The damaged tissue attracts platelets and they further exacerbate the endothelial cell response, leading to thrombosis in the vicinity of the stent. Compounds that can inhibit ISR and intimal hyperplasia are excellent candidates for drug eluting stents.

Table I gives a list of drugs in drug eluting stents.

Table I. Drugs used in drug eluting stents

Immuno-supessives	Anti-proliferative drugs	Migration inhibitors	Enhanced healing	Anti-thrombins
Sirolimus	Taxol (paclitaxel)	Batimastat	BCP671	Heparin
Tacrolimus	Actinomycin	Prolylhydrosylase inhibitors	VEGF	Hirudin and iloprost
Everolimus	Methotrexate	Halofunginone	17β-estradiol	Abciximab
Zotarolimus	Angiopeptin	C-proteinase inhibitors	NO donor compounds	
M-prednisolone	Vincristine	Probucol	EPC antibodies	
Dexamethasone	Mitomycin	Metalloproteinase inhibitors	TK-ase inhibition	
Cyclosporine	Statins		HMG CoA reductase inhibitors	
Mycophenolic acid	C-*myc* antisense		Biorest	
Mizoribine	Abbott ABT-578			
Interferon-1b	RestenASE			
Tranilast	2-Choloro-deoxyade nosine			
Leflunomide	BCP678			
Myolimus	Taxol derivative (QP-2)			
Novolimus	PCNA ribozyme			

Anti-proliferative drugs

Anti-proliferative compounds include paclitaxel, QP-2, actinomycin, statins and many others. Paclitaxel was originally used to inhibit tumor growth by assembling microtubules that prevent cells from dividing. It has recently been observed to attenuate neointimal growth as well.

Immunosupressives

These agents are generally used to prevent the immune rejection of allogeneic organ transplants. The general mechanism of action of most of these drugs is to stop cell cycle progression by inhibiting DNA synthesis. Everolimus, sirolimus, tacrolimus (FK-506), ABT-578, interferon, dexamethasone, and cyclosporine belong to this category. The sirolimus derived compounds appear to be promising in their ability to reduce intimal thickening.

Migration inhibitors

These compounds are aimed at preventing endothelial cell migration to the inside of the stent. Once smooth muscle cells migrate to the luminal side of the stent, they can produce an extracellular matrix and begin to occlude blood flow. Therefore, inhibiting their migration can have great therapeutic applications for preventing in the stent restenosis. Examples of these compounds are batimastat and halofuginone. Batimastat, for example, is a potent inhibitor of matrix metalloproteinase enzymes. It can prevent matrix degradation, which is necessary for cell migration and stent invasion. If the cells cannot move, they cannot invade the stent area.

Enhanced healing factors

Vascular endothelial growth factor promotes healing of the vasculature. In the context of stents, this would heal the implantation site and reduce platelet sequestration due to injury related chemotaxis. Nitrous oxide donor compounds may also replicate this effect. Healing of the vessel wall seems to be the gentlest approach to preventing ISR, but healing factors are still at the early stages of development for this application.

PRODUCTS OF DRUG-ELUTING STENTS

Stents eluting anti-inflammatory agents

Because of the role of inflammatory cells in restenosis, these cells seemed to be an optimal target in the fight against restenosis. Indeed, corticosteroids have long been shown to reduce the influx of mononuclear cells, to inhibit monocyte and macrophage function, and to influence smooth muscle cell proliferation (18). Nonetheless, clinical trials have failed to demonstrate any benefit of systemic steroid therapy (19).

Stents eluting corticosteroids

Methylprednisolone (300 mg) eluting tantalum stents coated with poly (organo) phosphazene were utilized in a porcine model. Although 96 % of the drug was released within 24 hours, a reduction in neointimal proliferation resulted; compared to intimal hyperplasia promoted by the polymer alone (20). Others did not observe the antirestenotic effect of stents loaded with 0.8 mg of dexamethasone in a similar model (21).

Tranilast-eluting stents

Tranilast, *N*-(3,4-dimethoxycinnamoyl) anthranilic acid, has been shown to inhibit proliferation and migration of vascular smooth muscle cells in experimental models. Systemic use of this agent for prevention of restenosis was tested in a large multicenter trial and it was observed that tranilast did not improve the targeted quantitative measure of restenosis, *i.e.*, angiographic and intravascular ultrasound or its subsequent clinical implications (22).

Stents eluting immunosuppressive agents

Encouraged by the early experience with ionizing radiation therapy, researchers have proposed sophisticated pharmacological strategies interfering with cell cycle division (10). Xenobiotic molecules (rapamycin, FK506, cyclosporine, and analogues) and antimetabolites (mycophenolate mofetil) have been utilized.

Sirolimus eluting stents. – Sirolimus is a macrolide antibiotic with potent antifungal, immunosuppressive, and antimitotic properties. The drug is produced by cultured *Streptomyces hyroscopicus.* Shortly after its approval, the first sirolimus-eluting stents were implanted in human coronary arteries.

Rapamycin analogue eluting stents. – Everolimus, [40-*O*-(2-hydroxyethyl)-rapamycin], is also an inhibitor of mTOR. It has been shown to inhibit proliferation of hematopoietic and non-hematopoietic cells. Although the immunosuppressive activity of everolimus is 2 to 3 fold lower than that of sirolimus *in vitro*, animal studies have shown a potent anti-restenotic effect of everolimus given orally or *via* a drug-eluting stent (23).

Tacrolimus eluting stents. – Tacrolimus is a hydrophobic immunosuppressive agent that has been used clinically to prevent renal transplant rejection. It binds to the FKBP12 protein, but its mechanism of action differs from sirolimus. Tacrolimus has been shown to inhibit the release of proinflammatory cytokines and activation of T cells. Initial *in vitro* and *in vivo* studies have failed to demonstrate the inhibition of smooth muscle cell proliferation with tacrolimus.

Mycophenolic acid-eluting stent. – Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil, an antibiotic derived from cultures of the *Penicillium* species, and has both antineoplastic and immunosuppressive properties. The Duraflex stent (Avantec Vascular Devices, USA), coated with a 5-µm layer of polyhydrocarbon polymer loaded with MPA, showed a 40 % reduction in neointimal proliferation compared to the control in a porcine coronary model (G. Leclerc, personal communication, 2002). The inhibition with MPA of the coronary restenosis trial (IMPACT) is a multicenter study that included 150 patients with *de novo* coronary lesions. Slow-release (45 days) and fast-release (15 days) eluting stents coated with 4.5 µg of MPA mm^2 were compared with bare Duraflex stents. Preliminary results suggest no differences in angiographic outcomes between groups, but final data are still pending.

Paclitaxel eluting stents

Paclitaxel is a microtubule stabilizing agent with potent antitumor activity. Many different platforms that use polymer coatings or surface modifications to cause paclitaxel to adhere onto the stents have been utilized over the past 2 years. Paclitaxel exerts its antiproliferative effects at concentrations much lower than those used for the treatment of cancer (24).

Angiopeptin eluting stents

Somatostatin, an angiopeptin analogue, has been shown to reduce tissue response to several growth factors. In humans, systemic administration of angiopeptin has improved the clinical outcome after angioplasty but showed no effect in restenosis (25).

Tyrosine kinase inhibitor eluting stents

The results of clinical studies on the use of these agents are awaited.

Actinomycin D-eluting stents

Actinomycin D is an anticancer drug that selectively inhibits RNA synthesis. Clinical trials using this drug were stopped prematurely because its use led to a high incidence of repeat revascularization.

Stents eluting anti-thrombotic agents

Though vessel injury with resulting platelet aggregation and thrombus formation plays a prominent role in the development of restenosis, antithrombotic pharmacological approaches have been proven to be ineffective in preventing restenosis. Nitrous oxide and glycoprotein IIb/IIIa inhibitors have been used as stent coatings, but their efficacy is yet to be proved (26).

Stents eluting extracellular matrix modulators

Matrix metalloproteinases (MMP) have the ability to digest collagen and facilitate smooth muscle cell migration. Batimastat, a non-specific MMP inhibitor, as well as other MMP inhibitors have been shown to inhibit neointimal hyperplasia in animal models (27). However, in human trials they have not shown significant benefits.

Stents eluting prohealing agents

There are reports suggesting that endothelialization of stents with a functional endothelium reduces the restenotic process (28). In a recent study, implantation of endothelial progenitor cell (EPC) capture stents showed promising results; there was no increase in major adverse cardiac and cerebrovascular events (MACCE) (29). Nitric oxide, vascular endothelial growth factor, and 17-ß-oestradiol have all been tested as prohealing and antirestenotic agents, but the results are conflicting.

FUTURE TRENDS

New solutions for the next generation of drug-eluting stents

Intense work on stent development has successfully led to the introduction of diverse DES (Fig. 2). Several critical breakthrough technologies account for the remarkable progress in the field of interventional cardiology in the past three decades: intracoronary stents have increased success rates and reduced restenosis, adjunctive antiplatelet therapy has reduced periprocedural complications, and restenosis after stent placement has been effectively treated with local radiation (30). The role of other agents with potential benefits (*e.g.* statins, adenovirus-mediated arterial gene transfer, tyrosine kinase inhibitors, L-arginine, abciximab, angiopeptin, r-PEG-hirudin and iloprost) as well as biodegradable stents may be tested in the future. The rapidly developing fields of nanotechnology, microelectronics, and advanced materials technology will enable the surface engineer to design molecular-specific surfaces for a new generation of vascular devices (31).

New coating (bioabsorbable coating). – Bioabsorbable DES is a device that could achieve excellent acute and long-term results, but disappear completely within months, thereby avoiding the need for prolonged dual antiplatelet therapy. In the late 1990s, a bioabsorbable (Igaki–Tamai, Japan) stent, made of a high-molecular-mass poly-L-lactic acid (PLLA), was implanted in 15 patients (25 stents) to evaluate the feasibility, safety, and efficacy of the PLLA stent. No major cardiac event, except for repeat angioplasty, developed within 6 months. Coronary PLLA biodegradable stents are feasible, safe, and effective in humans. Long-term follow-up with more patients is required to validate the long-term efficacy of PLLA stents (32). Everolimus eluting poly-L-lactide stent, which
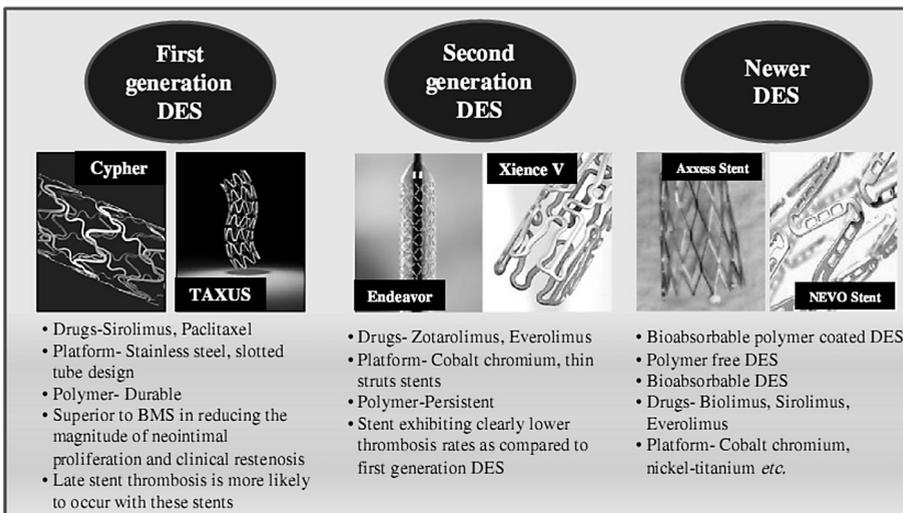

Fig. 2. Different generations of drug eluting stents.

demonstrated comparable restenotic rates with BMS and a low incidence of major adverse cardiac events, suggests that there has been significant progress compared to earlier prototypes (33, 34). Biotronik absorbable magnesium stent is the only stent in clinical trials (Table II). Unlike magnesium stents, there has been little progress with iron stents, which remain in the pre-clinical phase, and this may be partly due to the longer degradation time needed and potential issues related with iron clearance (35, 36).

Complete absorbable metallic or polymeric-free platform. – The use of polymer-free stents may have a potential long-term benefit over traditional polymeric coated DES. Tada *et al.* evaluated local delivery of Biolimus A9, from a polymer-free BioFreedom stent (Table II). BioFreedom (Biosenses, USA) stents were associated with reduced neointimal proliferation compared to the polymer coated sirolimus-eluting Cypher stent. The polymer-free Biolimus A9 coated stent demonstrates equivalent early and superior late reduction of intimal proliferation compared to the Cypher stent in a porcine model (37). Costa *et al.* (38) assessed the safety and efficacy of the novel VESTAsync-eluting stent (MIV Therapeutics, India) combining a stainless steel platform with a nanothin-microporous hydroxyapatite surface coating impregnated with a low polymer-free dose of sirolimus. The novel VESTAsync-eluting stent was effective in reducing lumen loss and neointimal hyperplasia, with no evidence of late catch-up by quantitative coronary angiography or intravascular ultrasound.

A new technique of elution (reservoir, dual elution). – Pimecrolimus, a tacrolimus analogue, has been investigated on its own, but also in combination with paclitael (Symbio stent, Conor Medsystems, USA). It exerts multiple anti-inflammatory effects including inhibition of IL-2 synthesis *via* calcineurin inhibition.

Prohealing approach + sirolimus or paclitaxel. – The Synchronnium stent (Sahajanand Medical Technologies, India) consists of a stainless steel stent coated with a biodegradable polymer incorporating heparin and sirolimus. Both drugs are released simultaneously over approximately 50 days. The initial clinical results are promising. Genistein, a natural isoflavanoid phytoestrogen is currently under investigation in combination with sirolimus. Flavanoids have a number of potentially beneficial characteristics including anti-platelet aggregation, anti-inflammatory and anti-oxidant properties.

Prohealing approach (endothelial progenitor cell (EPC) capture). – An alternative approach, concentrating on healing as opposed to SMC inhibition, is used in the Genous endothelial progenitor cell (EPC) capture stent (Orbus, Neich, USA). This is a stainless steel stent coated with murine monoclonal antihuman CD34 antibodies, which attract circulating EPCs, thereby encouraging rapid endothelialization and reducing thrombosis. The EPC capture stent appears effective in stable patients (39, 40) and also in the setting of acute myocardial infarction (41).

New stent design for challenging targets such as coronary bifurcations. – The OPTIMA new-generation DES system offers the combination of a polymer-free drug reservoir and Carbofilm coating. It has proven antithrombotic and potentially prohealing action. The OPTIMA (Carbostent and Implantable Devices [CID] S.r.l., Italy) key features are the absence of any polymer to carry the tacrolimus (the proprietary drug-release system with reservoirs on the outer surface of the stent), ensuring the drug release being only tar-

Table II. Products in the market

Rapamycin derivatives	Stent name	Company	Stent material/coating material	Principal trials	Approval
Sirolimus	Cypher	Cordis Corporation, Johnson & Johnson, USA	Stainless steel/permanent polymer (PEVA-PBMA)	FIM, RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS	CE/FDA (April, 2003)
	NEVO	Cordis Corporation, Johnson & Johnson, USA	Cobalt-Chromium/ bioabsorbable polymer (PLGA)	NEVO RES, NEVO RES II	
	Supralimus	Sahajanand Medical, India	Stainless steel/ bioabsorbable polymer (PLLA-PVP-PLGA)	SERIES I, SERIES III RUN IN	CE
	Supralimus Core	Sahajanand Medical, India	Cobalt Chromium/ bioabsorbable polymer (PLLA-PVP-PLGA)	–	–
	BTI	Bioabsorbable Therapeutic Inc., USA	Bioabsorbable polymer (PA & salicylic acid)	WHISPER	–
	Genous	Orbus Neich, Hong Kong	Staineless steel/Combo EPC capture antibodies, synbiosys polymer and sirolimus	REMEDEE	CE
	ReZolve SES	REVA Medical, USA	Tyrosine-derived ReZorb bioabsorbable polymer	–	–
	Yukon	Translumina, Germany	Stainless steel/none (microporous surface)	ISAR-TEST, ISAT-TEST 3&4, ISAR-PEACE	CE
	Exel	JW Medical, China	Stainless steel/bioabsorbable polymer (PLA)	–	Clinical trial
	CORACTO	Alvimedica, Turkey	Stainless steel/bioabsorbable polymer (PLGA)	–	Clinical trial
	VESTsyns	MIV Therapeutics, India	Stainless steel/nano-porous hydroxyapitate	–	Clinical trial
	Cardiomind	Cardiomind Inc., USA	Nitinol/bioabsorbable polymer (PLA, PLGA)	–	Clinical trial
Everolimus	Xience V	Abbot Vascular, USA	Cobalt-chromium/permanent polymer (PLDF-HFP)	SPIRIT I-IV	CE/FDA (July, 2008)
	Xience Prime	Abbot Vascular, USA	Cobalt-chromium/permanent polymer (SIBS)	SPIRIT PRIME	CE/FDA (November, 2011)
	Promus Element	Boston Scientific, USA	Platinum-chromium/permanent polymer (SIBS)	PLATINUM	CE

Table II. Cont.

	BVS	Abbot Vascular, USA	Bioabsorbable polymer (PLLA)/bioabsorbable polymer (PDLLA)	ABSORB, ABSORB EXTEND	–
Tacrolimus	Janus	Sorin Biomedical, Italy	Stainless steel/carbofilm(pyrolytic carbon)	JUPITER I–II	CE
	Optima	CID S.r.I, Italy	Stainless steel/carbofilm (pyrolytic carbon)	–	Clinical trial
	Maharoba	Kaneka, Japan	Cobalt-chromium/biodegradable polymer	–	Clinical trial
Zatarolimus	Endeavor ZES	Medtronic Vascular, USA	Cobalt-chromium/permanent polymer (PC)	ENDEAVOR I–IV	CE/FDA (February, 2008)
	Endeavor Resolute	Medtronic Vascular, USA	Cobalt-chromium/ bioabsorbable polymer (BioLinx:C19-pvp-C10)	RESOLUTE, RESOLUTE-AC, RESOLUTE-US	CE
Biolimus A9	Biomatrix	Biosensors, USA	Stainless steel/bioabsorbable polymer (PLLA)	STEALTH I, LEADERS	CE
	BioFreedom	Biosensors, USA	Stainless steel/none	BIOFREEDOM FIM	–
	Axxess	Devax Inc., USA	Nickel-titanium/bioabsorbale polymer (PLA)	–	Clinical trial
	Nobori	Terumo, Japan	Stainless steel/bioabsorbable polymer (PLLA)	NOBORI I–II	CE
	Custom NX	Xtent, USA	Cobalt-chromium/bioabsorbale polymer (PLA)	–	Clinical trial
Pimecrolimus	Corio	Conor, USA	Cobalt-chromium/ bioabsorbale polymer	–	–
	Dreams	Biotronik, Singapore	Absorbable metal stent 93 % magnesium and 7 % rare earth metals	–	Clinical trial
	Prolimus	Biotronik, Singapore	Cobalt-chromium/ bioabsorbale polymer	–	Clinical trial
Myolimus	DEsolve	Elixir Biomedical, Ireland	Cobalt-chromium/bioabsorbable polymer (PLA)	–	–
Novolimus	DESyne/ DESyne BD	Elixir Biomedical, Ireland	Cobalt-chromium/permanent polymer (N/A)	EXCELLA, EXCELLA II	–

Taxol derivatives

Paclitaxel	Taxus Express	Boston Scientific, USA	Stainless steel/permanent polymer (SIBS)	TAXUS I–IV	CE/FDA (March, 2004)
	ION/Taxus Liberte	Boston Scientific, USA	Stainless steel/permanent polymer (SIBS)	TAXUS IV–VI	CE/FDA (February, 2012)

Table II. Cont.

Taxus Element	Boston Scientific, USA	Platinum-chromium (N/A) /permanent polymer (SIBS)	PERSEUS	CE
Infinnium	Sahajanand Medical, India	Stainless steel/ bioabsorbable polymer (PLLA-PVP-PLGA)	SIMPLE I–II	CE
Costar	Conor, USA	Cobalt-chromium/ bioabsorbable Polymer	–	CE
Axxion	Biosensors, USA	Stainless steel/none	–	CE
REVA	REVA Medical Inc, USA	Tyrosine polycarbonate/ biodegradable polymer	–	Clinical trial
JACTAX HD	Boston Scientific, USA	Stainless steel/bioabsorbale polymer (DLPLA)	–	CE
Amazonia Pax	MINVASYS, France	Cobalt-chromium/polymer free stent	–	–

Others

Batimastat	BiodivYsio	Bio Compatibles, UK	–	BRILLIANT – I & II	–
Dexamethosone	BIodivYsio	Bio Compatibles, UK	–	STRIDE	–
Actinomycin D	Action	Guidant, USA	–	–	–
Resten NG	–	Medtronic, USA	–	–	–
Micophenolic acid (MPA)	–	Aventec, USA	–	–	–
Pimecrolimus + Paclitaxel	Symbio	Conor, USA	Cobalt-chromium/biodegradable polymer	–	–
Sirolimus + Heparin	Synchronnium	Sahajanand Medical, India	Stainless steel/biodegradable polymer	–	–
Zatrolimus + Dexamethasone	Zodiac	Abbott, USA	–	–	–
Sirolimus + Estradiol	–	Translumina, Germany	Stainless steel/none	–	–

FDA – Food and Drug Administration, CE – Conformite Europeene

geted toward the vessel wall. Integral Carbofilm coating favors early endothelialization of the stent thus reducing the risk of stent thrombosis (42).

New drug (less cytostatic or cytotoxic). – Batimastat is a broad spectrum MMP inhibitor, non-cytotoxic and thus potentially provided controlled antagonism of the restenosis process (43). Biocompatibles, a stent company (now owned by Abbott Vascular Devices, USA), applied batimastat to their phosphorylcholine (PC) coated Biodivysio stent. Another novel target is the local delivery of anti-VEGF, which might decrease the formation of vaso vasorum and thereby promote antheromatous plaque stability. Investigation into the anti-VEGF bevacizumab (Avastin) eluting BiodivYsio stent (Biocampatibles Ltd., UK) is currently in progress (44).

CONCLUSIONS

Intense work on stent development has successfully led to the introduction of drug-eluting stents in 2002, as an effort to address restenosis problem. First generation DES (sirolimus and paclitaxel eluting) was introduced first and found to be more effective than the bare metal stent (BMS). The use of the first generation DES dealt with the problem of restenosis. But, despite early successes, uncertainty remains in the overall safety, especially for late adverse clinical events such as stent thrombosis. Thus, the second generation (everolimus and zotarolimus eluting) stents were developed and introduced with lower thrombosis rates. Today, in the search for improving the performance of available DES, various developments and clinical studies are ongoing. The success of the present DES has shifted the focus to further development toward enhancing long-term safety and efficacy of these devices. The next generation DES will probably further improve endothelization and rapid arterial healing.

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S A Ž E T A K

Sadašnjost i budućnost stentova za restenozu koji otpuštaju lijekove

MAULIK J. PATEL, SANJAY S. PATEL, NIDHI S. PATEL i NATVARLAL M. PATEL

Stentovi koji otpuštaju lijekove (DESs) koriste se u kardiologiji za terapiju bolesti karotidnih arterija jer značajno smanjuju restenozu. Dobar DES ima polimerni sloj za isporuku lijekova. Klinički pokusi u kojima je ispitivano nekoliko agenasa pokazali su značajno smanjenje restenoze nakon ugradnje stenta. Razvoj DES-a jedno je od revolucionarnih otkrića u području interventne kardiologije. Idealni lijek za prevenciju restenoze mora imati antiproliferativni i antimigracijski učinak na stanice glatkih mišića, a s druge strane mora povećavati endotelizaciju kako bi se spriječila tromboza. Osim toga, treba učinkovito inhibirati protuupalni odgovor nakon ozljede arterije. Iako DES značajno smanjuje restenozu krvnih žila, kasna tromboza i restenoza ostaju i dalje problem i predmet brojnih istraživanja.

Ključne riječi: stent koji otpušta lijek, restenoza, biorazgradljivi polimer

Shri B. M. Shah College of Pharmaceutical Education and research, Modasa-383315, Gujarat, India