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RECENT ADVANCEMENT IN DEVELOPMENT OF DRUG ELUTING STENTS DELIVERY SYSTEM

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ABSTRACT

Cardiovascular diseases are one of the major causes of death in industrially developed countries. In particular occlusive pathologies of coronary and peripheral arteries are the third cause of death in these countries. The recent introduction of drug eluting stents (DES) technology contributes a major advancement in the treatment of obstructive coronary – artery diseases. A DES is a peripheral or coronary stent (scaffold) which slowly elutes a drug locally, design to limit the growth of neointimal scar tissue; thus reducing the likelihood of stent restenosis. In DES designing the Stent platform (metallic platform), Coating (a drug carrier vehicle which holds and elutes the drug in a controlled manner), Active therapeutic agent (reduces neointimal growth) are three major parts are used; for stent platform different type of metallic can be used like stainless steel, nitinol, cobalt, chromium, platinum, gold, magnesium alloy etc, and polymers which are generally used in DES are may be Biodegradable polymers (like poly lacticacid (PLA), poly glycolic acid (PLGA), poly caprolactone (PCL) etc. or Non biodegradable polymers (like polybutylmethacrylate (PBMA), polymethyl-methacrylate (PMMA), phosphorylcholine, polyethyleneterphthalate (PET) and the drug incorporated in the stent is basically Immunosuppressive and Antiproliferative drugs like Sirolimus, Everolimus, Zotarolimus, Paclitaxel etc. to inhibit neointimal growth which would cause restenosis. The success of DES in a long term clinical outcome basically depends upon Stent configuration, Strut Thickness, Stent coating, and Drug elution. Therefore, the introduction of DES in percutaneous coronary intervention (PCI) is a major innovative advancement in interventional cardiology. DES dramatically reduces the ISR rate in all subgroups of patients. Continuing improvement in drug delivery stent technologies and gradual reduction in cost makes DES an effective mainstay of therapy for CAD.

Key Words: Stent, Coating, Restenosis, Drug loading, Coronary artery disease (CAD).

INTRODUCTION

The traditional approach to treat blocked coronary arteries was coronary artery bypass graft surgery (CABG), In this, a section of vein or artery from elsewhere in the body is used to bypass the diseased segment of coronary artery. Andreas Gruntzig in 1977 introduced percutaneous trans luminal coronary angioplasty (PTCA), it is also called balloon angioplasty, in which a catheter was introduced through a peripheral artery and a balloon expanded to dilate the narrowed segment of artery. But the Balloon angioplasty however remain limited by abrupt vessel closure that necessitates emergency bypass surgery in 2-3 % of patients and restenosis that prompts repeat revascularization in 30-50 % of patient.[3] To overcome this problem, the concept of prosthetic devices inside the arteries to maintain the blood flow to the ischemic area came into existence by Dotter and Melvin Judkins[2]. One such device is “stent”, which is basically a small piece of metal “scaffolding” that

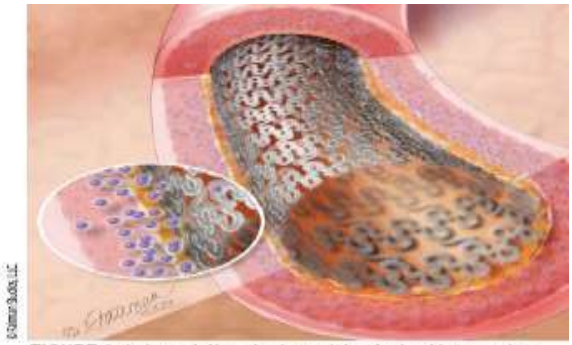

FIGURE 1. A drug-eluting stent consists of a backbone, a drug, and a polymer coating that controls the drug's release.

push arterial plaque to the side and provides a framework to keep the blood vessel open so that blood can flow freely through it and drug-eluting stent (DES) is a peripheral or coronary stent (a scaffold) placed into narrowed, diseased peripheral or coronary arteries that slowly releases a drug to block cell proliferation which may lead to neointimal scar tissue. This prevents fibrosis that, together with clots (thrombus), could otherwise block the stented

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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. Puel and Sigwart in 1986 implanted the first coronary stent in a human patient. In 1990s Several trials showed the superiority of stent placement over balloon angioplasty. Restenosis was reduced because the stent acted as a scaffold to hold open the dilated segment of artery; acute closure of the coronary artery (and the requirement for emergency CABG) was reduced, because the stent repaired dissections of the arterial wall. By 1999, stents was used in 84% of percutaneous coronary interventions (PCI) . Early difficulties with coronary stents included a risk of early thrombosis (clotting) resulting in occlusion of the stent. To overcome the risk of early thrombosis (clotting), coating of stent was introduced. Developers of DES used the devices themselves as a tool for delivering medication directly to the arterial vole. Coating stainless steel stents with other substances such as platinum or gold did eliminate this problem. High-pressure balloon expansion of the stent to ensure its full apposition to the arterial wall, combined with drug-therapy using aspirin and another inhibitor of platelet aggregation (usually ticlopidine or clopidogrel) nearly eliminated this risk of early stent thrombosis.

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 effects (MACE). Therefore the development of DES has been a major advance in the treatment of obstructive coronary artery disease. Many large randomized clinical trials using DES have shown a remarkable reduction in angiographic restenosis and target vessel revascularization.

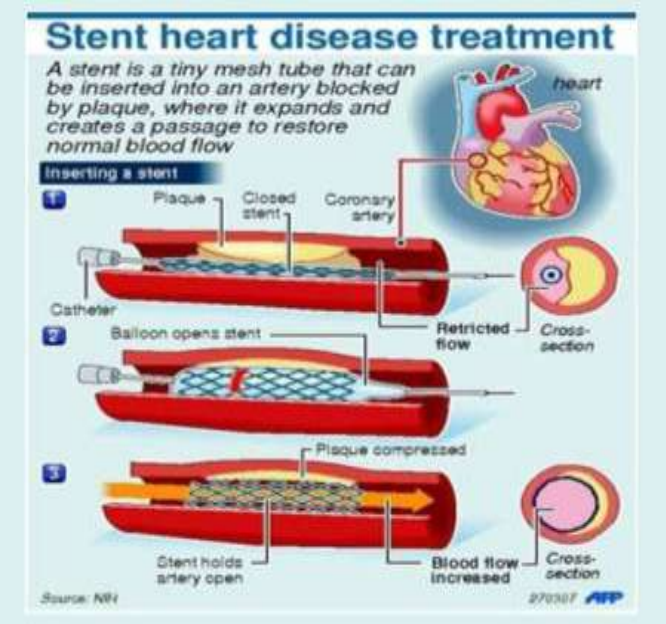


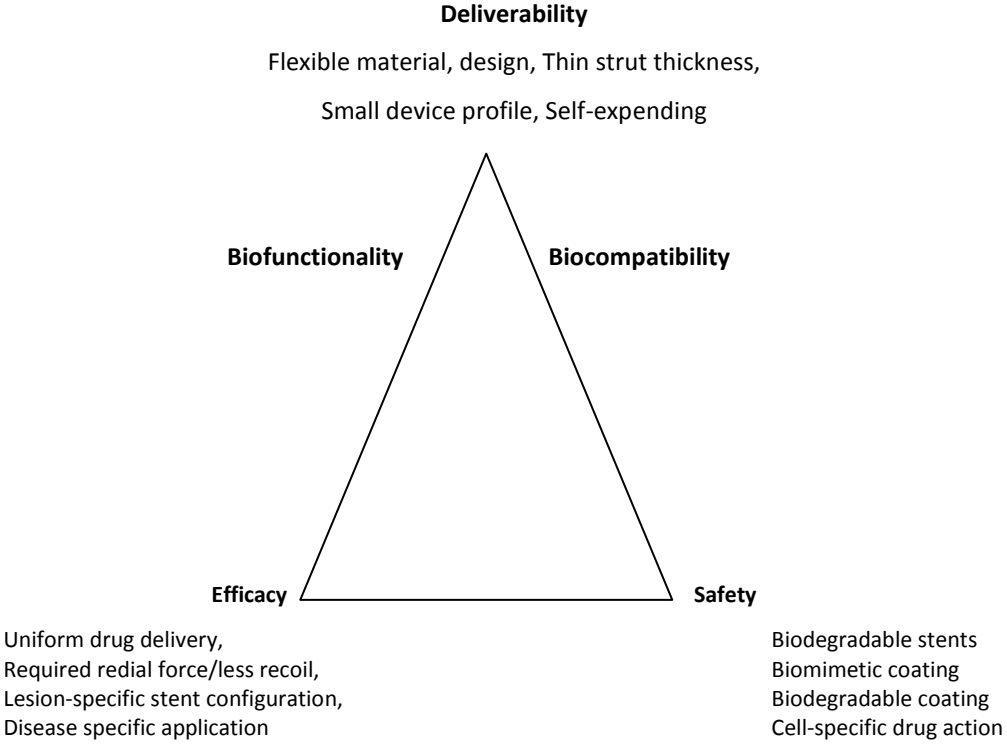
Figure-2

DESIGN AND CONFIGURATION OF DES

The main processes of in-process restenosis (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 three components: (1) **a metallic platform**, (2**) a drug carrier vehicle (or polymeric coating)** 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. Therefore, an ideal DES to achieve the greatest

clinical efficacy and safety is one that requires an optimization of these three essential parameters.

DESIGN CRITERIA FOR THE IDEAL DES



STENT PLATFORM

It is an expandable metal alloy framework, and have elaborate mesh-like designs to allow expansion, flexibility and in some cases the ability to make/enlarge side openings for side vessels. Different metals can be used in stent platform preparation.

Metals used as stent platforms

Stainless Steel : Iron based alloys, 1st generation DESs

- **Nitinol (Nickel + Titanium)** : Self expanding, shape memory low thrombogenic Radius Stent
- **Cobalt Chromium :** 2nd generation DESs, safe
- **Tantalum, Platinum, Gold:** Good radiopacity, marker for stents
- **Platinum Chromium:** New generation DESs
- **Magnesium alloy** : Biodegradable low strength

DRUG CARRIER VEHICLE

A coating, typically of a polymer, holds and elutes (releases) the drug into the arterial wall by contact transfer. Coatings are typically spray coated or dip coated. There can be one to three or more layers in the coating e.g. a base layer for adhesion, a main layer for holding the drug, and sometimes a top coat to slow down the release of the drug and extend its effect. Different type coating material have been used in DES preparation.

Coating materials

Biodegradable polymers: Biodegradable polymers have been developed to improve stent biocompatibility or to serve as a carrier for proliferation modulating drugs. Examples of biodegradable polymers (polyglycolic acid/polylactic acid [PGLA], polycaprolactone [PCL]polyhydroxybutyrate validate [PHBV], polyorthoester [POE] and polyethyleneoxide/polybotylene terephthalate [PEO/ PBTP]) est. That all of these compounds are coating material in DES. Therefore in all these biodegradable polymers can incorporate drugs and the drug eluting is achieved by disintegration of the biodegradable polymer of the stent.

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	BC671
Tacrolimus	Actinomycin	Proly!hydroxylase inhibitors	VEGF
Everolimus	Methotraxate	Halofunginone	Estrodiols
Leflunomide	Angiopeptin	C-proteinase inhibitors	No donor compounds
M-Prednisolone	Vincristine	Probucol	EPC antibodies
Dexamethasone	Mitomycine		Biorest
Interferon r-1b	Statins		
Mycophenolic acid	C-myc antisense		
Cyclosporine	RestenASE		
Tranilast	2-choloro-deoxyadenosine		
PCNA ribozyme			

Non-Biodegradable polymers: These compounds have been examined as direct surface coatings and as carriers of biologically active compounds. When non-biodegradable matrices are utilized, drug delivery is achieved through controlled release of the drug by diffusion through the porous matrix. The most extensively investigated polymers with many medical applications are polyurethane, silicone and polyethyleneterphthalate, Phosphorylcholine etc.

Membrane Covered Stents: A totally different method has been chosen in covering the entire stent with a polymer membrane. Using this technique, a polytetrafluoroethylene (PTFE) membrane is mounted between two stents. Although using this approach did not enhance the biocompatibility of the stent. Preliminary data suggest that this stent might be a superior treatment strategy in the special clinical setting of stenting of aortocoronary bypass grafts.

Metals as coating material:

Gold Coating: Gold is the noble metals and its high biocompatibility makes it a suitable coating material to use in many medical implants. It was found that coating of stainless steel with gold would ameliorate the biocompatibility of stents. In addition experimental data showed favourable results, especially with respect to thrombogenicity.

Carbon coating: In its pure form, carbon exists in two different crystallographic modifications, as diamond and graphite. Although experimental studies report that graphite enhances thrombogenicity[23], it is currently used as a surface coating for artificial heart valves[. Diamond can be used as a barrier coating to reduce metal ion release. Carbostent is the one another type of stent which is coated with pure carbon characterized by a polycrystalline structure.

Ceramic coating: Aluminium oxide coating with a unique nanoporous surface.

Therapeutic Agents:

Many agents with anti-inflammatory or antiproliferative properties have been incorporated on the stent surface and tested clinically.

APPROACHES FOR STENT COATING

Passive coating: Passive coating serves as barrier between the stainless steel and the tissue and is generally employed to achieve a more biocompatible stent surface. Passivation is the most important surface treatment for nitinol devices. It is normally achieved by dipping stents in a 10% nitric oxide solution. This treatment improves corrosion resistance due to an increased growth of TiO_2 on the stent surface. Other techniques of passive coatings to achieve a more biocompatible stent surface include synthetic or biological polymer deposition, ceramic (SiC) or carbon coating (CC).

Active coating: Present strategies for managing neointimal formation are all based on local drug delivery. The stent itself becomes an active device, eluting drugs at the lesion site. Active coating directly interferes with intima proliferation generally

based on the effects of drug. There can be one to three or more layers in the coating e.g:-a base layer for adhesion, a main layer for holding the drug and sometimes a top coat to slow down the release of drug and extend its effect. There are many advantages of the active coating (i.e. local elution of drugs): patients can be treated with high regional dosage while maintaining a low systemic drug concentration, so avoiding secondary effects and, moreover, drugs with relative low biological availability or short half-lives can be targeted directly at the lesion sites.

STENT ASSEMBLING TECHNIQUE:

Matrix Technique: In matrix strategy, combines the copolymers and antiproliferative agent in one phase. Drug release depends upon diffusion of drug through this inoculated layer of polymer.

Reservoir Technique: The second assembly technique called the reservoir technique begins with placement of the antiproliferative drug directly on the stent. Polymers are then added to the stent. Drug becomes accessible to the surrounding tissue after diffusing across the polymer phase.

Hybrid Technique: The third assembly technique is a hybrid between the matrix and reservoir. This stent design involves application of mixture phase consisting of the polymer and the drug which is then coated by a drug free layer of polymer.

The success of DES basically depends upon:

- Stent configuration
- Strut thickness
- Stent coating
- Drug elution mechanism

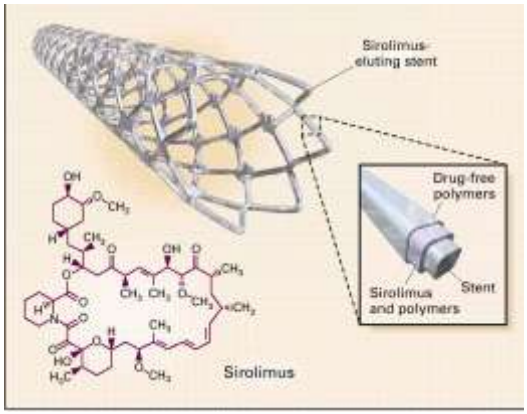


Figure-3: Framework of a typical Sirolimus Eluting Stent CYPHER™

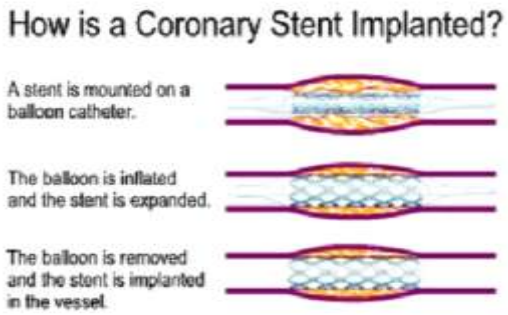


Figure-4: Schematic representation of implantation of coronary stent

SOME COMMERCIALLY AVAILABLE STENTS

- CYPHER™ (J&J, Cordis) uses a 316L stainless steel BxVelocity stent (140 µm struts) and adds a 12.6 µm 3 layer coating (2 µm Parylene C base coat, 10 µm main coat of PEVA, PBMA and sirolimus, and a 0.6 µm top coat of PBMA).] The sirolimus elutes over a period of about 30 days.
- TAXUS™ (Boston Scientific) uses a 316L stainless steel Express2 stent (132 µm struts) and adds a 16 µm single layer Translute SIBS copolymer coating containing paclitaxel which elutes over a period of about 90 days.
- ENDEAVOUR™ (Medtronic) uses a cobalt chrome Driver stent (91 µm struts) and adds a 4.3 µm phosphorylcholine coating that includes Zotarolimus, on a 1 µm base coat.
- XIENCE™ V (Guidant, Abbott) uses an L605 cobalt chrome ML Vision stent (81 µm struts) and adds a 7.6 µm fluropolymer multilayer coating with drug everolimus TaxCor (EuroCor GmbH) Highly Flexible Cobalt Chromium Stent Platform coated with fully biodegradable polymer as a carrier for Paclitaxel.
- INFINNIUM™ (Sahajanand Medical Technologies) Matrix Stent Platform contains biodegradable polymers as a drug delivery vehicle with Paclitaxel.
- AXXION™ (Biosensors Int) Stainless steel stent, Synthetic Glycocalix coating with paclitaxel.
- BIOMATRIX™ (Biosensors Int) S stent platform, bioabsorbable PLA coating with Biolimus A9 drug.

- ARTAX™ (Aachen Resonance) double helix stainless steel platform, without polymer, metal coated with paclitaxel drug.
- BIODIVYSIO™ (Biocompatibles Cardiovascular, UK) with phosphorylchoine coating.
- CARBOSTENT™ (Sorin Biomedica, Italy) with Ppyrolytic carbon coating.
- TENAX™ / Tensum III (Biotronik, Germany) with Silicon carbide coating.
- NIROYAL™ (Boston Scientific SciMed, U.S.A) with Gold coating.
- JOMED™ Coronory Stent Graft (Jomed, Sweden) with PTFE coating
- INFLOW™ (In Flow Dynamics AG, Germany) with Gold coating.

FUTURE PERSPECTIVES:

Although many attempts have been made to increase biocompatibility of coronary stents. The Ideal stent material and stent design are still a challenge for modern engineering and cardiology. As stent coating offers the opportunity to combine mechanical properties and biocompatibility of different materials, this is a promising direction for future research. In addition, the introduction of coated stents allows the intra vascular delivery of drugs for prevention of neointima formation and restenosis. Proof of the concept for stent-based drug delivery was demonstrated firstly in animal and then clinical studies. How promising these results might be, appropriately powered, randomized studies should confirm the current data before the chapter of restenosis in interventional cardiology can be closed.

CONCLUSION

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. New drugs or mixtures of drugs will probably be the answer to overcoming the ISR problem and we are just approaching the way to do that; at the same time, new molecular technologies such as antibodies seeding of luminal stent struts surfaces and antisense technology drugs to inhibit neointimal proliferation are adding chess pieces in our fight against ISR. 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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