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Review Article

A review on drug eluting stents

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ABSTRACT

Coronary artery disease (CAD) is currently a leading cause of health hazard worldwide. Drug-eluting stents (DESs) have been dominant for the treatment of coronary disease in the interventional cardiology world owing to their effectiveness and efficacy in significantly reducing restenosis and owing to requirement of the minimal invasive procedure. Initially Drug-eluting stents were developed with an idea to lower the rate of restenosis, which now occurs in less than 10 percent of patients treated with these stents. There have been rising concerns about abrupt thrombosis within drug-eluting stents occurring late after the implantation of the DES, which leads to acute myocardial infarction and death. Recent studies have tried to alleviate these concerns. Fair and adequate communication between cardiologists and primary care physicians is essential to avoid the premature discontinuation of therapy, and also to identify, those patients in whom prolonged therapy may be ill-advised. This review focuses on introducing the DES and describing the criteria for selecting a stent, new generations of drug-eluting stents based on the use of novel stent platforms, coatings, and carrier systems, developed to enhance DES safety along with the examples of various classes of DES among the most clinically-used DES. The review makes an effort to enlist the advantages and disadvantages of the conventional and newer generation of DES available and also a comparative study amongst all the three available generation of the DES along with the therapeutic effectiveness of the available stents and the risk associated with the stents.

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1. Introduction

A stent is an expandable mesh cylindrical device used to treat angioplasty to open blocked arteries of the heart (Stone et al., 2009). The stents are mounted on a balloon and inserted at the site of blockage, (Waksman et al., 2006) it works by expanding into the arterial wall as the balloon get inflated (Stone et al., 2009). The procedure includes a minimal invasive method wherein the balloon is being inserted with the help of a catheter into a peripheral artery from where it is guided to the blocked artery, where the inflated balloon compress the plaque against the wall of the blocked artery to re-establish the normal blood flow. After the blockage has been opened, the balloon is deflated and removed however the stent remain in place, by providing a scaffolding action to keep the artery open, for restoring hearts normal flow (Stone et al., 2009). The stent stays in the artery permanently and holds it open to improves blood flow in the heart muscle and relieves symptoms (usually chest pain). Within a couple week time the stent placed, the inside lining of the artery (the endothelium) grows over the metal surface of the stent.

Over the decades with huge advances having been made in areas such as invasive surgery and interventional cardiology, as a result cardiac patients have had the option of undergoing preventive measures against what could otherwise result in serious complications with angioplasty. In this sphere of invasive surgery, the "Coronary Stent" has been one of the most significant innovations (Tanimoto, 2008).

2. History

The first intracoronary stents were successfully deployed in coronary arteries in 1986. The first stents used were self-

-expanding Wall stents. Since then stent technology has improved rapidly, and 1989 the Palmaz-Schatz balloon-expandable intracoronary stent was developed. Coronary angioplasty - also known as percutaneous transluminal coronary angioplasty (PTCA) was first introduced in the 1970s as a minimally-invasive means of re-opening blocked coronary arteries. Bare-metal stents (BMS) were introduced in the mid-1990s with the aim of overcoming the deficiencies related to balloon angioplasty. The risk is that the blood clots due to the presence of a 'foreign body', forming a potentially life-threatening blockage (thrombus) to the artery. Drug-eluting stents were specially developed to address the problems of rest enosis encountered with BMS. In April 2003, the Food and Drug Administration approved the first ever drug-eluting stent in the United States, the sirolimus eluting Cypher TM stent. The first DES launched was the Cypher® stent in 2003, followed by the Taxus® stent in 2004 and the late 2000's a problem started to emerge with DES which hadn't been seen with BMS, that is of very late stent thrombosis here the thrombus was shown to form inside the stent more than a year after insertion, far later than usually observed with a BMS. The latest developments in DES technology are therefore understandably focusing on how to overcome the problem of late stent thrombosis, while retaining a superior clinical profile (Waksman et al., 2006).

3. Criteria for selection of a Stent

Balloon angioplasty is now rarely used alone, although it is often used to dilate the stenosis before stent placement. Two main factors that are considered when choosing between bare-metal or a drug-eluting stent. First, the presence of clinical or technical factors associated with an increased risk of restenosis; such patients are mostly benefited from drug-eluting stent. Multiple randomized trials have shown that drug-eluting stents provide good long-term outcomes than bare-metal stents in the following class of populations: patients with diabetes, long and/or complex stenoses, acute myocardial infarction (MI), in-stent restenosis of a bare-metal stent, and total coronary artery occlusions. Secondly, the patient's ability to comply with the necessary dual antiplatelet therapy. Patients with a history of poor compliance, an increased risk of bleeding, or those who need surgery or invasive procedures that would necessitate the premature withdrawal of antiplatelet therapy are often more profited by placement of a bare-metal stent because the duration of dual antiplatelet therapy is shorter. However, depending on the individual circumstances, surgical revascularization or further increasing the intensity of medical therapy may be appropriate (Bertrand et al., 1998 and Dehmer et al., 2009).

4. Risk associated with DES:

4.1. Incidence of In-Stent Restenosis

In-stent restenosis (ISR) due to the condition of occurrence of neointimal hyperplasia after stent implantation has plagued the field and has emerged as the Achilles' heel of this era of vascular interventions (Forrester et al., 1991). Stent placement in peripheral arteries is associated with a greater rate of ISR; it has been reported to occur as up to 40% of femoropopliteal lesions treated with bare-metal stents within 1 year of treatment.

ISR can be defined either clinically or angiographically. Clinically, it is defined as hemodynamically significant stenosis within a stent which may cause recurrent ischemia. Angiographic ally, it is defined as the presence of greater than 50% diameter of stenos is within a stent. Balloon angioplasty and stinting of an artery induces a localized inflammatory response, which precipitates neointimal proliferation and tissue growth.

The placement of a stent inhibits the artery's natural movement. Furthermore, current nitinol stent systems are oversized for its use in peripheral arteries and can result in chronic outward radial force that causes long-term inflammation. Thus, the placement of stent results in mechanical trauma to the walls of the artery, which triggers an inflammatory response (Forrester et al., 1991).

4.2. Stent Thrombosis

Acute stent thrombosis has been a major concern since bare metal stents were first introduced. The agents used in drug-eluting stents inhibit intimal and smooth muscle's growth after stent was placed, also inhibit the normal healing process whereby the stent is eventually covered by healthy endothelium. This leaves metal and polymer exposed to the blood, which may stimulate late thrombus formation after antiplatelet therapy is stopped.

A small number of patients treated with drug-eluting stents have shown increased cell death (apoptosis) in the artery wall behind the stent, results in formation small pockets in which blood stasis and thrombosis can occur (Forrester et al., 1991).

5. An Ideal Stent (Forrester et al., 1991)

5.1. An ideal stent should do its job and then disappear.

5.2. The ideal stent would be made of biocompatible material to prevent vessel irritation and collapsing as a result of any injury responses that occur following implantation.

5.3. With the stent gone after it does its job, late thrombosis should not occur and the stent would not interfere with CT or MRI evaluation.

5.4. A bioabsorbable or biodegradable stent satisfies all the requirements for an ideal stent.

5.5. These stents may prove to be the patient-preferred option. Patients have expressed that they would rather have an effective temporary implant as compared to a permanent prosthesis that often requires surgical removal

5.6. A disappearing stent would promote the restoration of the previously clogged or damaged artery to a "healthy artery," one that can endure the pressures of a normal artery.

5.7. A bioabsorbable stents is that they can be used to prevent further build up of plaque in arteries.

6. Different Bioabsorbable Stent Models

Bioabsorbable stents that are currently being developed are made of either polymers or corrodible metal alloys.

6.1. Polymeric Stents: There are several polymeric bioabsorbable stents that have been tested. The Igaki-Tamai coronary stent and the bioabsorbable everolimus-eluting coronary stent (BVS) use Poly-L-lactic acid (PLLA). Other bioabsorbable polymeric stents include ones developed by Bioabsorbable Therapeutics and the REVA Medical stent.

6.1.1. Igaki-Tamai: The Igaki-Tamai stent was the first ever bioabsorbable stent developed that was implanted in humans. The stent is made of PLLA, has a thickness of 0.17 mm, has a zigzag helical coil pattern, and is balloon-expandable. The study proved PLLA to be safe in human coronary arteries. In the study, no episode of stent thrombosis or no major cardiac event occurred within the first 6 months, that is there were no deaths, heart attacks, or coronary artery bypass surgeries. Full degradation took 18-24 months, the Igaki- Tamai stent lacked a drug coating, and since focus turned to bioabsorbable stents coated with drugs, the development of the Igaki-Tamai stent halted (Forrester et al., 1991; Shabto, 2014).

6.1.2. BVS stent: The BVS everolimus-eluting bioabsorbable PLL A stent is the first bioabsorbable stent to have clinical and imaging outcomes same as those following metallic DES implantation. The BVS stent has a polymer coating that contains as well as controls the release of the drug everolimus, which stops cells from reproducing by decreasing blood supply to the cells. In the study, 80% of the drug was released by the 30-day follow up. The thickness of the stent is 150 am. There was a decrease in blood vessel lumen diameter and higher-than-expected rest enosis rates. These initial results led to speculation that the absorption of the stent may have occurred too quickly. Full absorption of the stent was slow and took a period of 18 months. One major drawback is that there was an enlargement in the size of lumen, which was due to a decrease in plaque size without a change in vessel size (Forrester et al., 1991).

6.1.3. Bioabsorbable therapeutics: The polymeric stent developed by Bioabsorbable Therapeutics (BTI) is coated with a drug sirolimus, which suppresses the body's immune system. Both the base polymer and coating polymer of the stent are made up by forming bonds between salicylic acid molecules. These bonds are hydrolyzed during absorption, resulting in the release of salicylic acid, which could potentially prevent restenosis. The BTI stentis balloon-expandable and has a thickness of 200 μm. There is a significant thickening of the inner lining of the artery wall (Forrester et al., 1991).

6.1.4. REVA medical: The REVA Endovascular Study of a Bioresorbable Coronary Stent (RESORB) is coated with a drug paclitaxel, which inhibits cell division. The stent is balloon-expandable and is set into place by sliding and locking the parts which gives the stent more radial strength. The stent has a thickness of 150 μm. In a study conducted in 2008, between 4 and 6 months after implantation, showed that there was higher rate of occurrence of repeated PCI, driven mainly by reduced stent diameter (Forrester et al., 1991).

6.2. Metal alloy stents

Metal alloy bioabsorbable stents perform similarly to permanent metallic stents. Two bioabsorbable metal alloys that have been proposed for application are iron and magnesium. However, neither of these stents is coated with drugs.

6.2.1. Bioabsorbable magnesium stent: Magnesium stents have potential advantages over polymeric stents in terms of higher radial strength due to their metallic nature and biocompatibility as it is present as naturally occurring element in the body. This stent has a thickness of 165 μm and is balloon expandable. In a trial, the absorption of a magnesium stent in humans was rapid and mechanical support lasted for days to weeks, which is too short to prevent restenosis. During the first four months of the study, major adverse cardiac events were recorded in 24% of the patients and additional PCIs were needed after initial implantations. After a year, 45% of the patients reported additional PCI. The magnesium stent can be safely degraded within 4 months, but the high risk of restenosis rate raises concern (Forrester et al., 1991).

6.2.2. Bioabsorbable iron stent: Iron is one of the essential component of a variety of enzymes, making iron based alloys serves as a favorable material for bioabsorbable stents. The experimental iron stent has a thickness of 100–120 μm and is balloon-inflatable. The researchers implanted stents made of 41 mg of pure iron, amount equivalent to the monthly oral intake of iron for a healthy human, into the descending aortas of New Zealand white rabbits. During the 6 to 18 months of follow up, there was no report of occurance of thrombosis or any other significant inflammatory injury response. However, the animals experienced destruction of the internal elastic membrane of arteries and products from the degradation of the stent are accumulated, resulting in significant alteration of the artery wall (Shabto, 2014).

7. Generations of Drug Eluting Stents

7.1. 1st generation DES

First-generation DES includes sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). Since their introduction into worldwide clinical practice in the years 2003 and 2004, first-generation DES - Cypher (SES; Cordis Corporation, Johnson & Johnson, Warren, NJ, USA) and Taxus (PES; Boston Scientific Corporation, Natick, MA, USA) - have constantly reduced the cases of ISR and target vessel revascularization (TVR) across virtually all lesion and patient subsets compared with BMS. However, their safety has been questioned because of the suboptimal polymer biocompatibility leading to their susceptibility for late and very late ST, and local drug toxicity.

It was further identified that the durable polymers (DP) of these first-generation DES are the possible triggers for chronic vessel wall inflammation, delayed hypersensitivity reactions, delayed arterial healing, incomplete stent strut re-endothelialisation due to inhibition of endothelial cell proliferation, stent malapposition, accelerated neoatherosclerosis, and polymer-induced increased risk of very late ST (Ernst et al., 2014).

7.2. 2nd generation DES

The second-generation DES has focused mainly on enhancing deliverability over their first-generation versions. These includes the Endeavor (Medtronic, Minneapolis, MN, USA), Resolute (Medtronic), Xience V (Abbot Vascular, Santa Clara, CA, USA), and Promus (Boston Scientific, USA) stents, and utilize a more biocompatible DP. The Endeavor second-generation stents utilize a cobalt-chromium (CoCr) platform and a permanent phorylcholine polymer that facilitates the release of a drug sirolimus analogue, zotarolimus.

The main representative of second-generation absorbable-polymer family of DES is the BioMatrix stent (Biosensors International, Singapore), which utilizes a sirolimus analogue (Biolimus A9) and a biodegradable polylactic acid (PLA) polymer that completely dissolves over a 6-9 month period. CoCr, and later platinum chromium (PtCr), platforms used in second-generation DES permits similar radial strength, enabling a thinner strut design and thus significantly improved deliverability.

To improve DES safety, second-generation DES have more biocompatible DPs, or bioabsorbable polymers, which are eventually bioresorbed, rendering the stent surface similar to BMS free of a chronic inflammatory stimulation. Second-generation fluorinated DP-based CoCreverolimus-eluting stents (Xience V, Abbott Vascular, and Promus, Boston Scientific) and PtCreverolimus-eluting stents (Promus Element, Boston Scientific) have been associated with reduced rates of early, late, and very late ST.

7.3. 3rd generation DES

The third-generation devices have made rapid improvements with innovation in stent composition and design for dealing with complex lesions. Bioabsorbable Drug-Eluting Vascular Scaffolds (BVS) represent a new concept for providing transient vessel support with drug delivery capability but theoretically without the long-term limitations of metallic DES, such as permanent vessel caging and possible malapposition, risk of late ST, neoatherosclerosis, and local inflammation. BVS have the unique ability of restoration of vascular physiology along with anatomical integrity, such as native tortuosity and angulations, as it provides only a temporary scaffold necessary to maintain the patency of the vessel after intervention.

Currently, four materials are used in BVS, of which lactide polymers, particularly poly-levo-lactic acid (PLLA), other materials include magnesium, polyanhydrides (salicylic acid and adipic acid), and polycarbonates (amino acids, e.g. tyrosine).

A number of companies have stents with biodegradable polymers but under developmental stage, to-date there are only two widely available stents: BioMatrix™, launched in 2008; and Nobori, which uses the same polymer and drug license. The latest version of BioMatrix, the BioMatrix Flex™, launched in 2010, features more flexible stent platform for improved deliverability (Ernst et al., 2014).

8. Stent-based drug delivery system

The main processes of ISR is 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 is to locally deliver an appropriate amount of an effective agent to stop this process without systemic toxicity. An effective system consists of three components viz. (a) A metallic platform; (b) A drug carrier vehicle that stores a therapeutic agent and allows the agent to diffuse into the vascular tissue in a controlled fashion; and (c) An effective therapeutic agent which reduces the neointimal growth induced by stent implantation.

Therefore, an ideal DES has to achieve the greatest clinical efficacy and safety and is one that requires an optimization of the three essential parameters (Stone et al., 2007).

8.1. Design of Stent in relation to even drug distribution to vessel wall

The effect of different stent designs on the drug's distribution pattern has been tested in clinical trials and also scrutinized in experimental studies. The simple proximity of stent struts to vascular tissue does not ensure adequate drug delivery and uniform distribution because of its un-uniform distribution in the layers of the artery closest to the stent, 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 pattern of struts is essential for the optimization of drug distribution.

Although a large number of stent designs have been developed till date, only the multicellular design is most commonly used in current practice; they can be categorized into "closed cell" and "open cell" configurations. A closed cell stent has a constant cell spacing and regular cell expansion when deployed in a curved vascular segment, which gives more uniform drug distribution. An open cell stent has a greater variation in the surface between the inner and outer curvatures in the curved segment, but gives better conformability to curved surface at the expense of less homogeneous drug distribution. The majority of current BMS uses a closed cell design (Stone et al., 2007).

8.2. Therapeutic agents to inhibit neointimal growth

Many agents with anti-inflammatory or anti-proliferative properties have been incorporated on the stent surface and are tested clinically. Many of the agents have more than one mechanism of action. The general mechanism of action for most of these drugs used is to stop cell cycle progression by inhibiting synthesis of DNA. Everolimus, sirolimus, tacrolimus (FK-506), ABT-578, interferon, dexamethasone, and cyclosporine all follow same mechanism. Sirolimus and its derivatives were shown to reduce intimal thickening. Dexamethasone-coated BiodivYsio stent also showed a mild to moderate effect in reducing restenosis. Paclitaxel and ABT-578 has been approved for clinical use and appears promising. Angiopeptin and c-mycantisense also has been tested in clinical trials. Migration inhibitors (e.g., batimastat) are used for preventing smooth muscle cell from migrating into the inner side of the stent. Examples of these compounds are batimastat and halofuginone. Batimastat inhibits matrix metalloproteinase enzymes and thereby prevents the matrix degradation, which is necessary for cells to free themselves to move and invade the stent area. Enhanced healing factors

promote healing of the stent implantation site by reducing platelet aggregation and by increasing the rate of re-endothelialization. Estradiols and nitric oxide donor compounds may also replicate this effect.

Only two antiproliferative agents, sirolimus and paclitaxel, have been proved to be effective in clinical trials. Sirolimus (rapamycin), a fermentation product of *Streptomyces hygroscopicus*, is an antifungal macrolide antibiotic with potent immunosuppressive properties. Sirolimus is a lipophilic molecule and readily diffuses across the cell membranes of vascular smooth muscle cells and leukocytes. In the cytoplasm, it binds with high affinity to a specific intracellular protein (FKBP12), and the resultant complex inhibits a regulatory enzyme, called TOR (target of rapamycin) which ultimately blocks cell cycle progression from G1 to S phase, and in turn limits smooth muscle replication and proliferation.

Paclitaxel is an antineoplastic agent originally isolated from the bark of the Pacific yew tree, *Taxus brevifolia*. It was approved by FDA for treatment of breast and ovarian cancer in 1992. It is a lipophilic molecule that readily diffuses across cell membranes and has a potent stabilizing effect on microtubules. Since microtubule disassembly is essential for the progression of the G2 to M phase in the mitotic cell cycle, stabilization of microtubule inhibits the mitosis of smooth muscle cell and inhibits the cell migration. This reduces the infiltration of vascular smooth muscle cells and leukocytes into the site of injury caused by stent (Stone et al., 2007).

8.3. Safety and Efficacy of Drug-Eluting Stents in Older Patients With Chronic Kidney Disease(CKD)

In a large national cohort study of Medicare beneficiaries undergoing PCIs, has found that 40% of older patients undergoing PCIs have CKD. A strong and independent graded association between increasing severity of CKD and increasing cardiovascular events was observed. Patients with normal renal function and most subgroups of CKD those received a DES had significantly shown lower mortality rates throughout 30 months of follow-up. The benefits of DES with regard to MI, revascularization, and major bleeding were present in a large number, but not all, subgroup. This is the largest registry study to date which suggests that DES appear to be safe in older patients with varying levels of CKD undergoing PCIs (Tsai, 2011; Foley et al., 1998; Luft, 2000; Lysaght, 2002).

8.4. Concern relating stent thrombosis after drug-eluting stent implantation in acute myocardial infarction

One of the major concerns about DES implantation in AMI patients is acute, sub acute, late, and very late stent thrombosis, which may induce high episodes of cardiac death. Delayed arterial healing, chronic inflammation, late malapposition, and incomplete re-endothelialization are among the possible mechanisms for causing stent thrombosis. The stent size to place in AMI is decided in relation with enormous amounts of thrombosis and vasoconstriction. If a stent smaller than the vessel diameter is chosen it may cause malapposition of stents later that can result in late stent thrombosis. In the AMI patients, plaque rupture is involved in many cases and AMI patients treated with the first-generation and had later stent thrombosis in comparison with patients with stable lesions (Nakazawa et al., 2008). It was also shown that direct coverage of stent struts in lipidonecrotic core prevented appropriate plaque recovery and reendothelialization that is usually completed in up to 6 months in patients treated with BMS but remained incomplete after 40 months in case of patients treated with DES (Joner et al., 2006). Recently, in-stent neoatherosclerosis has been focused on as a cause of late-phase stent thrombosis as well as of in-stent restenosis after implantation of both DES and BMS (Cauda et al., 2008). The development of neoatherosclerosis as a cause of stent thrombosis is more important in DES than in BMS, because it occurs much earlier after implantation of the stents.

9. Types of Stent coatings:

9.1. Heparin

Heparin is a highly-sulfated glycosamino which is widely used in medicine for a number of clinical indications, predominantly anticoagulation. Due to its relative safety, high negative charge and existing use as an anti-adhesive coating on blood-related tubing and devices, the molecule has been used to urinary stents and tested for its ability in reducing biofilm formation and encrustation. In addition to the heparin coating, this stent possesses thermo sensitive properties that allow more rigidity during placement followed by its softening once exposed to body temperature, promoting higher patient comfort. An initial study involving two patients with stents indwelling for 10 and 12 months showed no encrustation and no changes in the heparin layer, suggesting that it might be a useful tool for long-term urinary drainage (Cauda et al., 2008). However, a subsequent *in vitro* study by Lange et al. (Lange et al., 2009) failed to show any benefitting result for the heparin-coated device over controls in resisting bacterial adherence. Therefore, further studies need to be conducted to determine whether stents with a heparin coating have potential as long-term devices able to resist both encrustation and biofilm formation *in vivo*.

9.2. Diamond-like carbon coatings

The first description of its application on urological devices was in 2004 by Dr. Norbert Laube's research group (Laube, 2004) at the University of Bonn, Germany. They applied a plasma-deposited, diamond-like amorphous carbon material to segments of both urethral catheters and urethral stents and demonstrated the preliminary efficacy in reducing encrustation and its ease of insertion. Based upon its overall nanocrystalline structure, outer monomolecular layer of non-polar hydrogen atoms and thin film application, the coating is chemically inert, biocompatible, lubricious and extremely durable. That initial work was followed by both *in vitro* and *in vivo* studies published in 2007 that demonstrated great promise in reducing patient symptoms, infections and encrustation (Laube et al., 2006; Laube et al., 2007). In latter conducted study involved with 10 chronically-stented patients suffering from numerous underlying disorders and requiring frequent stent changes due largely to heavy encrustation. Several different types of uncoated, polyurethane Double J stents were coated and 26 devices placed for a total of almost 2500 days across this population, the overall results showed decreased encrustation, biofilm formation, patient symptoms and complications, and also increased physician ease in device

handling, placement and removal. Further studies should target patients with short-term disease to investigate whether significant decreases in infection rates can be achieved in this population.

9.3. Teflon

Another coating displaying superlubricious properties is polytetrafluoroethylene (PTFE), also known as Teflon. The strongly hydrophobic compound has been long used as a non-stick surface and lubricant in a plethora of applications, from non-stick frying pans to lubricants, seals and insulation in rocket tanks and telescopes used by NASA. PTFE's coefficient of friction (0.05-0.1) is lowest of any known substance, behind only aluminum-magnesium-boron polymers (0.02) and rivaling those of diamond-like carbon compounds (0.05-0.2). Furthermore, its resistance to van der Waals forces, used by bacteria for initial surface attachment, in resisting bacterial colonization and biofilm development. While numerous in vitro studies conducted over the past decades have shown Teflon-coated surfaces to reduce protein adherence and bacterial attachment compared with the controls, other studies have found that some proteins and bacteria, mostly those with strong hydrophobic properties, are not affected (Lopez et al., 1991; Elayarajah et al., 2011). Chung et al. (Chung et al., 2008) tested PTFE-covered metallic stents and found that they prevent hyperplasia in comparison to non-covered devices in a canine ureter model device.

9.4. Hydrophilic coatings

Hydrophilic coatings have been well explored as coating alternatives for stent because of their hydrophilic properties, which act as a deterrent to hydrophobic bacterial surfaces and encrusting deposits within the urine. Polyethylene glycol (PEG) is a commonly used hydrophilic coating because of its success as an antifouling agent, a result of its high degree of mobility and steric hindrance in chemical structure (Morra, 2000). The structure of this polyether allows it to couple with numerous other water molecules, reducing its coefficient of friction and driving its fluid-like behavior. Research into PEG coating has demonstrated resistance to bacterial, protein and mammalian cell attachment (Dalsin et al., 2005), suggesting that PEG may be capable of resisting conditioning film development. Problems with PEG arise in its inability to anchor enough molecules to generate a dense coating and the prevention of its thermal, oxidative, or hydrolytic degradation during the anchoring process. To overcome these drawbacks researchers have developed novel approaches for attaching PEG to surfaces with the use of 3,4-dihydroxyphenylalanine (DOPA), a mimicking peptide based on the adhesive proteins used by mussels for attachment in marine environments (Waite et al., 1980). Through *in vitro* and *in vivo* studies DOPA conjugated PEG has been proven to be effective; demonstrating inhibition of both conditioning film and biofilm development (Ko et al., 2008), along with a significant reduction in uropathogenic *E. coli* adherence in a rabbit model of cystitis (Pechey et al., 2009). More recently, Liu and colleagues (Liu et al., 2011) demonstrated the suitability of PEG as a coating agent in paclitaxel-eluting stents. In 2007, John and his colleagues (John et al., 2007) demonstrated that hydrophilic gel (hydrogel) coated stent segments did not reduce bacterial adhesion compared to control.

9.5. Silver

Silver has been widely used as an antimicrobial agent for a long time, from preventing food spoilage by ancient civilizations, to prevent and treat wound infections, to its current use in the eyes of newborn babies immediately following delivery. One advantage of silver is that while it exhibits broad-spectrum antimicrobial activity, it lacks the concomitant host toxicity. Silver is known to cause bacterial membrane destabilization and to strongly bind with numerous bacterial enzymes, abolishing their activity (Slawson et al., 1992). Furthermore, Liu et al. (lie et al., 2011) indicated that silver alloy-coated catheters may increase the risk of developing urethral structures following robotic-assisted laparoscopic radical prostatectomy as compared to uncoated controls. Collectively, the overall lack of a definitive stance on the efficacy of silver in the urinary tract, coupled with the slightly higher cost of Ag-coated catheters, has resulted largely in indifferent and inconsistent use of the devices as well as a lack of incorporation of iron into current stent coating technologies.

9.6. Antimicrobial peptides

Antimicrobial peptides are of small molecular weight and with broad-spectrum antimicrobial activity against bacteria, fungi and viruses. Antimicrobial peptides are very diverse in both their structure and mechanism of action. RNAIII-inhibiting peptide (RIP) is a heptapeptide that is effective in the treatment of polymicrobial, as well as drug-resistant infections. In Staphylococcus aureus, RIP has been demonstrated to down regulate expression of genes involved in both biofilm formation and toxin production; while up regulating genes involved in stress responses and inhibiting cell-to-cell communication (Lopez et al., 2010). RIP-coated ureteral stent segments implanted in rat bladders have been shown to reduce both adherence to the stent and survival of planktonic cells by 99% when compared to that of uncoated controls (Cirioni et al., 2007). Another alternative that is yet to be studied for urological applications is melamine, a synthetically derived antimicrobial peptide, that incorporates the active regions of protamine (from salmon sperm) and melittin (from bee venom) (Wilcox et al., 2008). Melamine is effective against both Gram positive and negative bacteria and has been documented to retain activity when covalently attached to contact lenses in vitro (Yang et al., 2015).

10. Stents with special functions

10.1. Paclitaxel-eluting stent

Paclitaxel interferes with cell proliferation in the G0/G1 and G2/M phases of the cell cycle, and triggers molecular signaling, via the mitochondrial pathway, causing cell apoptosis (Kalinowski et al., 2002; Rowinsky and Donehower, 1995; Dhanikula and Panchagnula, 1999). Paclitaxel also causes the dose-dependent inhibition of cell proliferation of human epithelial gallbladder cells, human fibroblasts, and pancreatic carcinoma cells (Kalinowski et al., 2002).This inhibitory effect, observed in cell lines, has become the pillar for theoretical foundation for the development of drug-eluting stents for the use in malignant biliary strictures. Lee et al developed a metallic stent covered with a paclitaxel incorporated membrane (MSCPM-I), and the safety of this

device was proved in the porcine bile duct. After 4 weeks of period, the segment of bile duct containing the stent was examined histologically (Kabanov et al., 2002; Isayama et al., 2010). Epithelial denudation, mucin hypersecretion, and epithelial metaplasia were present in the bile ducts, but transmural necrosis and perforation were not observed in any treated animal. Another animal study also demonstrated the safety efficacy of paclitaxel-eluting SEMSs. In this study, endoscopically inserted paclitaxel-eluting covered metallic stents (PECMSs) and conventionally covered metal stents (CMSs) were studied in canine bile ducts. The PECMS group had mucosal hyperplasia and the stented segments were significantly thicker, these changes were not observed in the group with CMS. Through these animal studies, paclitaxel-eluting SEMSs were established as the foundation for developing a safe and new treatment modality for malignant biliary obstruction (Kim et al., 2014; Jeong et al., 2015). Paclitaxel is a suitable drug for its use in drug-eluting membranes, due to its pharmacokinetic characteristics, that is its hydrophobic nature and rapid cellular uptake (Liu et al., 2012).

10.2. Gemcitabine-eluting stent

Gemcitabine is the standard chemotherapeutic agent in advanced pancreatic and biliary tract cancer (Burris et al., 1997; Eckel et al., 2007). Gemcitabine is hydrophilic in nature and its local delivery is difficult due to the initial burst of the drug. Consequently, efforts have been made to control this (Moon et al., 2011; Lee et al., 2012). Pullulan is a natural polysaccharide that can be acetylated to varying degrees to form pullulan acetate, which has a greater drug-loading capacity. When pullulan acetate was layered in PTFE and applied as part of a gemcitabine-loaded controlled-release membrane in drug-eluting nonvascular stents, gemcitabine was shown to release for 30 days (Groen et al., 1987). *In vitro* and *in vivo* safety study was done in animal using porcine bile ducts, with a gemcitabine-eluting membrane that had been produced by another research team, by using a different method. A gemcitabine-eluting SEMS composed of three layers was inserted surgically with gemcitabine concentrations of 0%, 10%, 15%, and 20% (weight/volume). Histological examinations that were performed 4 weeks later revealed moderate to severe inflammation in the bile ducts in contact with the stents containing 15% and 20% of gemcitabine, but mild inflammation was observed with 10% of gemcitabine. Each of the groups showed an equivalent response in terms of fibrous reactions in the submucosal layer. No transmural necrosis or perforation was observed in any animal used. However, there have been no human clinical studies and so the safety and efficacy in humans has yet been validated (Groen et al., 1987).

10.3. Anti-reflux metal stent

Stents inserted into the biliary tract can be obstructed by biliary sludge, consisting of crystals of calcium bilirubinate and calcium palmitate, as well as proteins, mucopolysaccharides, cholesterol crystals, and bacteria (Groen et al., 1987; Sung et al., 1993; vanBerkel et al., 2005). When a biliary stent is inserted via the transampullary route, networks of large dietary fibers are formed because of duodenobiliary reflux; this intraluminal framework plays a prominent role in the multifactorial process of stent clogging. Accordingly, many studies have focused on improving the stent patency through the use of an ant reflux biliary stent, designed to suppress duodenobiliary reflux (Dua et al., 2007; Hu et al., 2011; Hu et al., 2014; Lee et al., 2013; Hamada et al., 2014; kim et al., 2013). In a human study, the median patency of this antireflux plastic stent was 145 (range 52–252) days, which was 52 Gastrointestinal Intervention (vanBerkel et al., 2005; Dua et al., 2007; Hu et al., 2011; Hu et al., 2014; Lee et al., 2013) significantly longer than the 101 (range 41–210) days seen with conventional plastic stents (Jang and Lee, 2015).

11. Conclusion

Based on the available data it can be concluded that the newer 3rd Gen biocompatible drug eluting stents maintain the efficacy standard as compared to the traditional metallic stents. However, and disappointingly, with respect to safety endpoints, second-generation biodegradable polymer-based DES fell short of high expectations. However, these devices still have limited applications, and till date they do not outperform the current generation of high performance metallic drug-eluting devices. Evidence from the validation study of the second-generation DES indicates that they have overcome the drawbacks of the first-generation (such as rapid bioresorption and device shrinkage) and that they can compete with the metallic stents in terms of safety and efficacy.

Finally, when assessing the efficacy and safety of a DES, biodegradability of polymer, the optimal combination of stent alloy, design, strut thickness, polymer, and the drug are the parameters which affect the stents performance. Nonetheless, however important the quality as well as performance of DES may seem, stents are only one of many, often underestimated but complex and critically pertinent, interplaying factors influencing the individual clinical outcome. Thus, effective management of patients who are undergoing percutaneous coronary intervention requires focus on clinical and angiographic data to guide optimal device choice in the continuously expanding scenario of coronary stents.

Conflict of Interest

Authors report no conflict of interest.

Reference:

Bertrand OF, Sipehia R, Mongrain R, Rodés J, Tardif JC, Bilodeau L, Côté G, Bourassa MG. Biocompatibility aspects of new stent technology. J Am Coll Cardiol. 1998; 32:562-571.

Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR. Improvements in survival and clinical benefit with gemcitabine as firstline therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997; 15:2403-2413.

Cauda F, Cauda V, Fiori C, Onida B, Garrone E. Heparin coating on ureteral double stents prevents encrustations: an in vivo case study. J Endourol. 2008; 22: 465-742.

Chung HH, Lee SH, Cho SB, Park HS, Kim YS, Kang B. Comparison of a new polytetrafluoroethylene-covered metallic stent to a noncovered stent in canine ureters. Cardiovasc Interv Radiol. 2008; 31:619-628.

Cirioni O, Giacometti A, Kamysz W, Silvestri C, Riva A, Della Vittoria A. In vitro activities of the antimicrobial peptide tachyplesin III against Pseudomonas aeruginosa. Peptides 2007; 28: 747-751.

Dalsin JL, Lin L, Tosatti S, Voros J, Textor M, Messersmith PB. Protein resistance of titanium oxide surfaces modified by biologically inspired mPEG-DOPA. Langmuir 2005; 21: 640-646.

Dehmer GJ, Smith KJ. Drug-Eluting Coronary Artery Stents. Am Fam Physician. 2009; 80: 1246-1251.

Dhanikula AB, Panchagnula R. Localized paclitaxel delivery. Int J Pharm. 1999; 183: 85-100.

Dua KS, Reddy ND, Rao VG, Banerjee R, Medda B, Lang I. Impact of reducing duodenobiliary reflux on biliary stent patency: an in vitro evaluation and a prospective randomized clinical trial that used a biliary stent with an antireflux valve. Gastrointest Endosc. 2007; 65: 819-828.

Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer. 2007; 96: 896-902.

Elayarajah B, Rajendran R, Venkatrajah B, Janiga PK. Prevention of biofilm formation on norfloxacin metronidazole treated ureteral latex stents. Int J Eng Sci Technol. 2011; 3: 544-551.

Ernst A, Bulum J. New Generations of Drug-Eluting Stents - A Brief Review. Eur Med J Int Cardiol. 2014; 1: 100-106.

Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. J Am SocNephrol. 1998; 9: 16-23.

Forrester JS, Fishbein M, Helfant R, Fagin J. A paradigm for restenosis based on cell biology: clues for the development of new preventive therapies. J Am Coll Cardiol. 1991; 17: 758-769.

Groen AK, Out T, Huibregtse K, Delzenne B, Hoek FJ, Tytgat GN. Characterization of the content of occluded biliary endoprostheses. Endoscopy. 1987; 19: 57- 59.

Hamada T, Isayama H, Nakai Y, Kogure H, Togawa O, Kawakubo K. Novel antireflux covered metal stent for recurrent occlusion of biliary metal stents: a pilot study. Dig Endosc. 2014; 26: 264-269.

Hu B, Wang TT, Shi ZM, Wang SZ, Lu R, Pan YM. A novel antireflux metal stent for the palliation of biliary malignancies: a pilot feasibility study (with video). Gastrointest Endosc. 2011; 73: 143-148.

Hu B, Wang TT, Wu J, Shi ZM, Gao DJ, Pan YM. Antireflux stents to reduce the risk of cholangitis in patients with malignant biliary strictures: a randomized trial. Endoscopy. 2014; 46: 120-126.

Isayama H, Kawabe T, Nakai Y, Ito Y, Togawa O, Kogure H. Management of distal malignant biliary obstruction with the ComVi stent, a new covered metallic stent. Surg Endosc. 2010; 24: 131-137.

Jang S, Lee DL. Stents with specialized functions: drug-eluting stents and stents with antireflux devices, Gastrointest Interv 2015; 4:50-54.

Jeong D, Lee DH, Lee DK, Na K. Nonvascular drug-eluting stent coated with sodium caprate-incorporated polyurethane for the efficient penetration of paclitaxel into tumor tissue. J Biomater. Appl. 2015; 29: 1133-1144.

John T, Rajpurkar A, Smith G, Fairfax M, Triest J. Antibiotic pretreatment of hydrogel ureteral stent. J Endourol. 2007; 21: 1211-1216.

Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, Kutys R, Skorija K, Gold HK, Virmani R. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol. 2006; 48: 193-202.

Kabanov AV, Batrakova EV, Alakhov VY. Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. J Control Release. 2002; 82: 189-212.

Kalinowski M, Alfke H, Kleb B, Dürfeld F, Joachim Wagner H. Paclitaxel inhibits proliferation of cell lines responsible for metal stent obstruction: possible topical application in malignant bile duct obstructions. Invest Radiol. 2002; 37: 399-404.

Kim DU, Kwon CI, Kang DH, Ko KH, Hong SP. New antireflux self-expandable metal stent for malignant lower biliary obstruction: in vitro and in vivo preliminary study. Dig Endosc. 2013; 25: 60-66.

Kim SY, Kim M, Kim MK, Lee H, Lee DK, Lee DH. Paclitaxel-eluting nanofiber-covered self-expanding nonvascular stent for palliative chemotherapy of gastrointestinal cancer and its related stenosis. Biomed Microdevices. 2014; 16: 897-904.

Ko R, Cadieux PA, Dalsin JL, Lee BP, Elwood CN, Razvi H. First prize: novel uropathogenresistant coatings inspired by marine mussels. J Endourol. 2008; 22: 1153-1160.

Lange D, Elwood CN, Choi K, Hendlin K, Monga M, Chew BH. Uropathogen interaction with the surface of urological stents using different surface properties. J Urol. 2009; 182:1194-2000.

Laube N, Bradenahl J, Meissner AV, Rappard J, Kleinen L, Mu¨ller SC. Plasma-deposited carbon coating on urological indwelling catheters: preventing formation of encrustations and consecutive complications. Urol A. 2006; 45: 1163-1164.

Laube N, Kleinen L, Bradenhal J, Meissner A. Diamond-like carbon coatings on ureteral stents: a new strategy for decreasing the formation of crystalline bacterial biofilms. J Urol. 2007; 177: 1923-1927.

Laube N. Diamonds are a urologist's best friend. 2004. Available from: http://www.eurekalert.org/pub_releases/2004-11/uob-daa111804.php. [Last accessed 08 November 2004].

Lee JW, Yang SG, Na K. Gemcitabine-releasing polymeric films for covered self expandable metallic stent in treatment of gastrointestinal cancer. Int J Pharm. 2012; 427: 276-283.

Lee KJ, Chung MJ, Park JY, Lee DH, Jung S, Bang BW. Clinical advantages of a metal stent with an S-shaped anti-reflux valve in malignant biliary obstruction. Dig Endosc. 2013; 25: 308-312.

Liu R, Wolinsky JB, Catalano PJ, Chirieac LR, Wagner AJ, Grinstaff MW. Paclitaxel-eluting polymer film reduces locoregional recurrence and improves survival in a recurrent sarcoma model: a novel investigational therapy. Ann Surg Oncol. 2012; 19: 199-206.

Liu XS, Zola JC, McGinnis DE, Squadrito JF, Zeltser IS. Do silver alloy-coated catheters increase risk of urethral strictures after robotic-assisted laparoscopic radical prostatectomy. Urology. 2011; 78: 365-367.

Lopez G, Pascual A, Perea EJ. Effect of plastic catheter material on bacterial adherence and viability. J Med Microbiol. 1991; 34: 349-353.

Lopez-Leban F, Kiran MD, Wolcott R, Balaban N. Molecular mechanisms of RIP, an effective inhibitor of chronic infections. Int J Artif Organs. 2010; 33: 582-589.

Luft FC. Renal disease as a risk factor for cardiovascular disease. Basic Res Cardiol. 2000; 9: 172- 176.

Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol. 2002; 13: 37-40.

Moon S, Yang SG, Na K. An acetylated polysaccharide-PTFE membrane-covered stent for the delivery of gemcitabine for treatment of gastrointestinal cancer and related stenosis. Biomater. 2011; 32: 3603-610.

Morra M. On the molecular basis of fouling resistance. J Biomater.Sci. 2000; 11: 547-569.

Nakazawa G, Finn AV, Joner M, Ladich E, Kutys R, Mont EK, Gold HK, Burke AP, Kolodgie FD, Virmani R. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation. 2008; 118: 1138-1145.

Pechey A, Elwood CN, Wignall GR, Dalsin JL, Lee BP, Vanjecek M . Anti-adhesive coating and clearance of device associated uropathogenic *Escherichia coli* cystitis. J Urol. 2009; 182: 1628-1636.

Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Eng J Med. 1995; 332: 1004– 1014.

Shabto J. Bioabsorbable Coronary Stents. Dartmouth Undergraduate J Sci. 2014; 14-16.

Slawson RM, Van Dyke MI, Lee H, Trevors JT. Germanium and silver resistance, accumulation, and toxicity in microorganisms. Plasmid. 1992; 27: 72-79.

Stone GW, Lansky AJ, Pocock SJ. Paclitaxel-Eluting Stents versus Bare-Metal Stents in Acute Myocardial Infarction. N Eng J Med. 2009; 360: 1946-1959.

Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Eng J Med. 2007; 356: 998-1008.

Sung JY, Leung JW, Shaffer EA, Lam K, Costerton JW. Bacterial biofilm, brown pigment stone and blockage of biliary stents. J Gastroenterol Hepatol. 1993; 8: 28–34.

Tanimoto S. Late stent recoil of the bioabsorbable everolimus-eluting coronary stent and its relationship with plaque morphology. J Am Coll Cardiol. 2008; 52: 1616–1620.

Tsai TT. Safety and Efficacy of Drug-Eluting Stents in Older Patients With Chronic Kidney Disease A Report From the Linked CathPCI Registry–CMS Claims Database. J Am Coll Cardiol. 2011; 58: 1859–1869.

vanBerkel AM, van Marle J, Groen AK, Bruno MJ. Mechanisms of biliary stent clogging: confocal laser scanning and scanning electron microscopy. Endoscopy. 2005; 37: 729–734.

Waite JH, Tanzer ML. The bioadhesivev Mytilus byssus: a protein containing L-dopa. Biochem Biophys Res Commun. 1980; 96: 1554-1561.

Waksman R. Safety and efficacy of bioabsorbable magnesium alloy stents in porcine coronary arteries. Catheter and Cardiovasc Interv. 2006; 68: 607-617.

Wilcox MDP, Hume EBH, Aliwarga Y, Kumar N, Cole N. A novel cationic-peptide coating for the prevention of microbial colonization on contact lenses. J Appl Microbiol. 2008; 105: 1817-1825.

Yang L,Whiteside S, Peter A.John DC. Denstedt, Ureteral stent technology: Drug-eluting stents and stent coatings. Asian J Urol. 2015; 2: 194-201.

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