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The Metamorphosis of Vascular Stents: Passive Structures to Smart Devices

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Drug-eluting stents (DES) represent a major milestone in stent technology, saving the lives of millions worldwide afflicted with cardiovascular disease. Though a wide range of therapeutic approaches has been employed for treatment of coronary artery diseases, stent deployment has become the most extensively practiced method to open blocked arteries in comparison with surgical revascularisation. In recent years, the bare metal stent has evolved into more effective drug-eluting systems and the encouraging results from initial clinical trials have instilled hope among cardiologists to reduce the number of fatalities caused by cardiovascular diseases through the deployment of drug-eluting stents. Over the years, the stents have evolved from being a passive framework that maintained blood flow through the blood vessels into multi-functional devices that could also serve to mitigate conditions leading to the blockage of the blood vessels while promoting re-endothelialization of the blood vessel. This review traces the evolution of the stents from the first generation structures to the modern versions that overcome their limitations. A glimpse into the exciting future of the stent technology is also provided.

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1. Introduction

Coronary artery disease is a major cardiovascular disorder that develops due to escalation of lipid oxidation. The oxidized products get deposited in the sub-endothelial space of coronary artery leading to atherosclerosis.[1] This results in a complex synergy between blood components leading to disruption in blood flow, artery wall irregularities, and other pathological conditions such as inflammation with monocyte accumulation, proliferation of smooth muscle cells and thrombosis upon platelet activation and fibrin formation. These manifestations cause severe obstruction of arteries, paving way for a spectrum of clinical events ranging from angina, myocardial infarction to sudden cardiac arrest.[2] Among the leading causes of death around the globe, coronary artery diseases top the list accounting for 35% fatality.[3] Treatment of cardiovascular disorders is highly invasive and the odds of survival are also minimal.[4] Traditionally, balloon angioplasty has been used to treat obstructed arteries, but this strategy is limited due to tearing of the vessel wall, causing acute vessel closure. It results from the disruption of the plaques by the expanding balloon, weakening the artery and also induce damage to the inner layers of the artery leading to deep intimal arterial injury contributing to restenosis at a later date.[5] To avoid such occurrences, a permanent metal framework known as stent is inserted through a blocked artery, which gives support to the artery as well as preserves the integrity of the vessels.[6]

Bare metal stent (BMS) are considered to be advancement over conventionally employed balloon angioplasty for the treatment of coronary artery diseases. Bare metal stents were the first to be approved by the Food & Drug Administration (FDA) and were considered highly efficient for reopening blocked arteries.[2] The BMS is fabricated as a typical mesh-like metal thin tube called as struts.[7] Stents are used as a frame to support the artery walls and confine the plaques to the wall.[6] Metals like stainless steel, cobalt- chromium, platinum and titanium possess sufficient strength to undergo plastic deformation thereby preventing the collapse of the artery due to the force imposed during stent implantation apart from restoring the original dimensions of the atherosclerotic artery.[6] BMS prevents restenosis through suppression of early arterial recoil and reduction of contraction as well as reduce tearing of vascular space through sealing the dissection.[8] However, stents being non-native to the body, are recognized as foreign objects and the immune system mounts a cascade of immune and inflammatory reactions at the time of implantation rendering the stent thrombogenic and non-biocompatible.[9] It has been observed that about 10-20% patients every year suffer from restenosis due to excess proliferation of the neointima.[10] Neointima is the inflammatory and proliferative reaction of the vessel wall to the injury created by angioplasty and stenting. The proliferative response is a normal healing process which includes smooth muscle proliferation and endothelial coverage of stent struts making the stent non-thrombogenic. But the quantum of neointimal proliferation becomes excessive in many individuals, causing narrowing of the opened artery , which results in-stent restenosis. None of the newer alloys could mitigate the problem of restenosis. These limitations have resulted in the emergence of drug eluting stents (DES) that act as a localized drug delivery system to mitigate the adverse effects of a bare metallic stent.

Drug eluting stents (DES) use a wide variety of pharmacological agents such as anti-proliferative and anti-inflammatory drugs namely sirolimus, paclitaxel, resveratrol and curcumin are coated on the metal stent using a polymer coating. The polymers commonly employed include the biostable polymers such as poly(ethylene-co-butyl methacrylate), poly(styrene-isobutylene-styrene) and phosphorylcholine as well as biodegradable polymers like polylactic acid, poly(L-lactide-co-glycolic acid[11] as a carrier. DES has shown promising results in retarding the rate of in-stent restenosis as well as inflammatory response.[12] DES has made major headway in the field of cardiovascular intervention

by reducing post-stenting complications such as restenosis or neointimal hyperplasia as well as the need for subsequent surgical interventions. It has enabled site-specific controlled drug release, which inhibits intimal hyperplasia and provides positive remodeling to the stenosed artery.[13] However, since the appearance of first-generation drug eluting stents, a new complication namely thrombosis, has emerged due to the excess accumulation of platelets and enhanced fibrolytic processes at the stent site. This has raised concerns on the safety and efficacy of DES.

Diverse strategies involving modification of the coating material, stent material, stent design, drugs employed, etc., have been attempted to overcome several drawbacks of the DES in order to develop more robust delivery systems. Several novel approaches in DES are also under different phases of pre-clinical and clinical trials. The present review attempts to explore the various advances in the field of stent technology including the different types of stents, their merits and demerits, on going research and development in drug eluting stents and emerging generation of 'smart stents' that will be discussed in the following sections.

2. Evolution of stent materials

Metals are the most commonly employed material for stents due to their strength and stability. Mechanical and physical characteristics of metals such as high toughness and fatigue strength apart from possessing corrosion- and abrasion-resistance have contributed to their use for various load-bearing implants. Stents are a type of vascular implants that require a durable scaffold that can reinforce the weak vessel wall, resist continuous pressure and in addition be biocompatible in the vascular space. Conventionally metals are the main choice for a stent material.[2] Based on the their characteristic features, safety and responsive nature, different metals and their alloys have been employed for the fabrication of a stent.[2] The earliest and most common stent material has been the alloy, stainless steel.[2] Other materials that have been used for fabricating stents include alloys like cobalt-chromium, platinum-iridium, and nitinol. Pure metals like gold, magnesium and titanium has also been used for making stents.[2] Other alternative non-metallic materials that have been employed as stent materials are biodegradable polymers.[2]

2.1 Stainless steel coronary stent

316L stainless steel has been the traditional choice of material for fabrication of bare metal stents.[14] Steel could potentially react with the biological system and undergo corrosion in the physiological conditions but stainless steel, an alloy of steel combines high strength, formability and corrosion resistance with a broad range of mechanical properties thereby making it an excellent choice of material for stents.[15] It also has a high radial strength and its ductility enables fabrication of stents with thinner strut dimensions. Stainless steel stents generally possess ultimate tensile strengths between 600-1000 MPa depending on their composition.[16] The tensile strengths of many iron-based stents that also possess degradation properties range from 200-500 MPa. Several iron-based stents alloyed with platinum possess tensile strengths as high as 1500 MPa. [17] Since stainless steel is alloyed to various metals such as nickel, chromium and molybdenum, their release can trigger a local immune response.[2] In case of stent, struts design play an important role for endothelialization but due to poor strength of stainless steel it restricts the dimensions of the struts that could be fabricated using this alloy leads to restenosis.[18] In addition, their ferromagnetic nature makes them non-MRI (magnetic resonance imaging) compatible.[19]

2.2 Cobalt-chromium stent

Cobalt-chromium is an advanced alloy that is stronger and denser than stainless steel. The tensile strength of cobalt-chromium stents generally lies between 800-1200 MPa.[16] Due to their

inherent strength, stents with thinner struts can be fabricated without compromising their radiopacity.[2] Thinner struts enable superior tissue coverage due to better endothelialization.[18] Such design is not feasible with stainless steel owing to its poorer strength. Cobalt-chromium alloy also possesses better fatigue-resistance, which leads to excellent radial strength and is more corrosion-resistant than stainless steel.[19] In addition, they possess high non-ferromagnetic property and hence the cobalt-chromium alloys are more MRI compatible than stainless steel.[20] However, fatigue fracture is one of the common disadvantages of such alloy-based stents.[19]

2.3 Platinum-iridium stent

Apart from corrosion resistance and stability, platinum metal has also been found to be biocompatible and radiopaque that makes it an excellent candidate for biomedical applications.[21] But the prohibitive cost of platinum limits its widespread use. Therefore various platinum alloys have been developed such as platinum-iridium, rhodium, palladium and ruthenium. Among these noble metal alloys. Platinum-iridium shows qualities for a stent material such good radiopacity, corrosion resistance, low inflammatory response hemocompatibility and biocompatibility.[22] However, lack of strength limits its application as a stent material as its recoiling percentage is higher as compared to stainless steel stent.[2]

2.4 Titanium stent

Titanium has been used extensively for biomedical applications such as in artificial hip and knee joints, cardiac valve prostheses, screws used for fracture fixation, bone plates, pacemakers, etc.[2] Biocompatibility, low electronic conductivity, stability at physiological pH and corrosion resistance are the main characteristics of titanium, which makes it a promising candidate for coronary stents.[23] However, titanium has low tensile strength and low ductility that may increase the chance of stents to fail under stress test during deployment. By alloying with other metals, the mechanical properties of titanium can be improved.[24] Stents made from various titanium alloys have tensile strengths ranging from 300-1000 MPa [16]

2.5 Nitinol stent

Nitinol is a nickel-titanium alloy with shape memory property and has been used to develop self-expanding stents.[25] Nitinol stents have been found to be super-elastic; crush recoverable and more physiologically compatible than balloon expandable bare metal stents.[26] The shape setting property of nitinol lowers the risk of damage to the stent both during the deployment into the body and at the time of vessel recoil.[2] The major drawbacks of this material are its high cost and increased metal fatigue, which leads to its failure due to bending or twisting.[27] Another issue with nitinol stents is its bulky delivery system, which makes it difficult to track through tortuous vessels. Currently Nitinol is used in the manufacture of the self expanding stents used in peripheral arteries and aorta. Figure 1. summarizes the major merits and demerits of the commonly employed metallic stents.

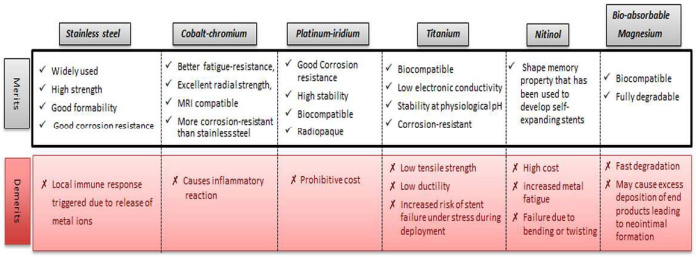

Figure 1. Outline the different types of stent material that have emerged with time along with their shortcomings.

2.6.Other stent materials

Tantalum is a promising material for many biomedical applications especially as scaffolds for orthopaedic and dental applications.[28] Tantalum causes low inflammatory response and has negligible dissolution properties. [28] It possesses excellent strength, ductile properties and biocompatibility that have been useful for designing

scaffolds for load-bearing tissues like bone.[16] **Tantalum stents** have been used as a substitute for platinum stents because of their high corrosion resistance and chemical inertness due to the highly stable oxide layer.[29] In addition, they are more cost-effective than platinum.[30] Tantalum alloys are widely used for medical implants due to their biocompatibility and non-irritating nature. Non-irritating stents cause no inflammatory responses thereby avoiding adverse effects such as vessel spasms.[31] However, their poor mechanical properties limit their application, as there exists an increased possibility of material fracture during stent deployment.[2] Also, stent recoil has been observed in tantalum-based stents when compared to stainless steel stents.[2] **Gold** is one of the least reactive metal found in nature and it is biocompatible as well as a blood compatible material with higher radiopacity.[32] These properties make it well suited as a stent material. However, improper gold coating during galvanization leads to surface defects during the stent manufacture because of which no significant difference in the performance of these stents were observed in clinical trials when compared to other stents.[33] Kastrati *et al.,* have demonstrated that gold stents increase the risk of restenosis and target vessel revascularization over the first year of stent placement.[34] Hence, these stents are rarely used in the present era**.** However in recent years, many approaches have been made to improve the performance of bare metal stents. Nanotechnology-enabled techniques like nanotexturing and nanopatterning have emerged, which could enhance the drug release efficiency of the stent surface. In addition, novel metal alloys such as platinum-chromium have been explored for stenting applications due to their better mechanical properties and radiopacity. [35]

2.7.Covered stents

Covered stent is a unique, flexible, biocompatible metal stent with an extra layer of membrane covering the stent completely or partially.[36] It is a multipurpose stent design that can be used for cardiovascular, neurovascular and peripheral interventions.[37,38] Covered stents represent an improved version of stent-grafts. They reduce fibrosis that is commonly encountered in bare metal stents.[39] The covered stent acts as a physical barrier that reduces the blockages occurring due to tissue in-growth and overcomes several limitations of other categories of stents.[40] These membranes can be effective against restenosis by preventing direct contact of the metal with the biological tissues.[41] Mechanical properties of the membrane material also are key factors that determine the performance of a covered stent. Biostable polymers such as poly(styrene-*b*-isobutylene-*b*-styrene) (SIBS),[42] expanded poly(tetrafluoroethylene) (ePTFE) and silicon membranes [43] have been the most successful materials for covered stents.[40] Natural and modified polymers have also been explored extensively for use in covered stents.[41,44] Chitosan-based polymers (Polyethylene oxide CH-PEO), PVA (polyvinyl alcohol) cryogel membranes, Polyethylene terephthalate (PET) or segmented polyether polyurethane (SPP) (SPU), bio-inspired salmon collagen fibrillar gel, heparin-impregnated collagen stent-graft, etc., have been used as coatings on stents.[45-47]

Covered stents face many clinical challenges when it comes to a small vascular treatment and aneurysms. They possess the risk of promoting thrombosis, hyperplasia and have been reported to prolong the healing process.[48] Hence, a novel technique employing a drug-loaded membrane coating on metal stent was introduced to overcome the limitations of covered stents. The drug releases gradually from the polymer membrane thereby achieving localized delivery at the target site that serves to mitigate any possible toxic effects arising due to the introduction of the covered stent. **Table 1** describes the different types of covered stent systems that have been reported for the treatment of various conditions. Although the covered stent is superior to other stents it displays high risk of stent migration, perforation, tissue in-growth or hyperplasia.[49] To overcome the problem of stent migration, partially covered stents have been developed with broad uncovered ends as dumbbells to

grip on to the tissue to impart better migration-resistance to the stents.[40] (Figure 2.)

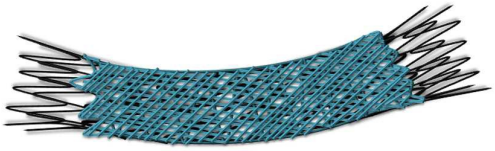

Figure 2. Schematic representation of a partially covered stent.

Table 1. Different types of covered stents used in cardiovascular complications.

Stents	Application
Covered stent graft	Treatment of *de novo* or traumatic arterial aneurysms and pseudo-aneurysms.[46]
Membrane-covered Express Monorail stents	Treatment of aneurysms, therapy for complications arising due to sealing coronary perforations.[47]
Paclitaxel-loaded poly (-caprolactone) electrospun fibrous membrane covered stent	Treatment of benign cardiac strictures to avoid inflammation and scar formation.[48]
Heparin loaded poly (L-lactide-co-caprolactone) nanofibre covered stent	Treatment of aneurysm.[50]

Fabric stents are a type of covered stents and are endovascular stent grafts. They are commonly used for the treatment of aneurysms and they provide support to the collapsing vessels. It is a permanent graft and consists of a metal stent (Nitinol, stainless steel or cobalt-chromium) fitted with a fabric made up of woven polyester (PET, Dacron), expanded polytetrafluorethylene (ePTFE) and polyether type polyurethane which serves as a membrane to support the inner wall of vessels and prevent it from rupture and maintains pulsatile blood pressure.[51,52]

3. Evolution of drug eluting stents from bare metal stents

Drug eluting stents (DES) represent the first breakthrough advancement in stent technology, as they were primarily designed to prevent high rates of restenosis encountered in bare metal stents. Delivering drugs directly to the target site reduces further stent-related complications associated with coronary artery disease.[53] Typically, DES consists of a bare metal backbone with thin polymer coating containing a drug formulation. The superiority of drug eluting stents in reducing in-stent restenosis in comparison with bare metal stents has been established beyond doubt through animal experiments and large clinical trials. Regardless of the fact that DES has transformed the field of interventional cardiology, certain stent-related complications mar its successes. The anti-proliferative drug in the DES restricts the intimal growth and migration of smooth muscle cells thus preventing restenosis, but it also inhibits endothelialization of the stent surface.[54] The resulting exposed stent surface increases the risk of thrombosis at the implant site. Clinical data reveals that the first drug eluting stents loaded with Sirolimus and Paclitaxel as anti-proliferative drugs though successful in limiting the growth of vascular smooth muscle cells, also impaired the endothelial cell proliferation leading to incomplete neointimal coverage and eventually stent thrombosis.[55] The polymer coating also may activate the immune response that in turn cause inflammation and in-stent restenosis as well as stent thrombosis at the site of deployment.[56] Therefore, an ideal drug for DES should promote rapid development of a normal endothelial lining of the stented vessel segment and prevent the proliferation of vascular smooth muscle cells (VSMCs) without hindering the healing process of endothelial cells. Many drugs and drug combinations are under active investigation to achieve desired repair and action. Many new classes of drug eluting stents have emerged based on the drugs employed and these represent the next generation drug eluting stents.[57]

4. Progress in choice of drugs for DES

Drugs that possess anti-proliferative, anti-inflammatory, anti-thrombotic or immunosuppressive properties have been employed as pharmacological agents in drug eluting stents. These drugs are loaded in to polymers that are coated on the stents and are released by either degradation of the polymer in the case of biodegradable coatings or through diffusion through the polymer chains in the case of a bio-stable coating. These drugs have diverse molecular targets to exert their anti-proliferative or anti-inflammatory property. These targets include mTOR pathway, NF-κB, calcineurin, cyclooxygenases, p27, P-selectin etc. (**Figure 3**.)

4.1. Anti-proliferative drugs used in DES

4.1.1 Sirolimus

Sirolimus (rapamycin) belongs to the class of natural macrocyclic lactones and has been found to be a potent immunosuppressive and anti-proliferative agent that binds to an intracellular receptor protein and eventually induces cell-cycle arrest.[12] It also retards vascular smooth cell migration, proliferation and growth through inhibition of Mammalian target of rapamycin (mTOR).[58,59]

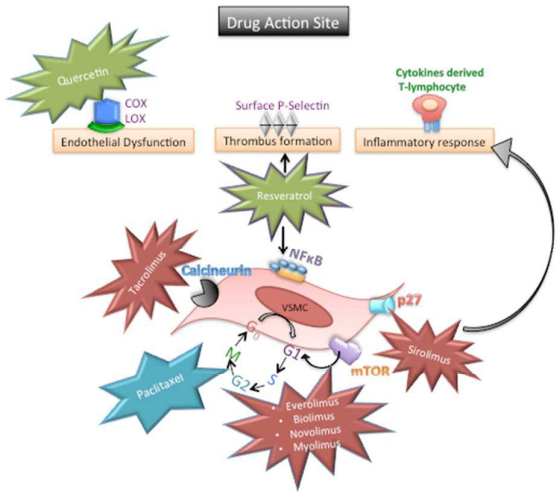

Figure 3. Depicts the major sites of drugs action used in stents. COX: cyclooxygenase, LOX: lipoxygenase, NF-κB: nuclear factor-κB, VSMC; Vascular smooth muscle cells, mTOR: mammalian target of rapamycin.

Extensive studies and numerous clinical trials have demonstrated that sirolimus can retard the proliferation of smooth muscle cells of both rat and human origin *in vitro*. It also effectively decreased the thickness of the intima in animal models of vascular injury.[12] Commercially available sirolimus eluting stents CYPHER (Company-Cordis, Platform Bx VELOCITY™), have been subjected to clinical trials (RAVEL and European SIRIUS) that revealed their high anti-proliferation activity and ability to decrease major adverse cardiac events (MACE). Significant reduction in neointimal hyperplasia was also observed due to the deployment of sirolimus eluting stent.[60] But their slow release profile and inability to promote re-endothelialization results in stent thrombosis, which could negate their clinical significance of reducing restenosis as compared to bare metal stent.[61]

4.1.2. Sirolimus analogues

The initial success with sirolimus had triggered a search of sirolimus analogues that possess similar anti-proliferative effect but lesser adverse effects. Among these analogues, everolimus (a new macrocylic triene derivative), biolimus A9, immunosuppressive agents such as cyclosporine, mycophenolic

acid and tacrolimus, which induce G1 arrest leading to reduced proliferation and immune response, have been incorporated in stents.[10] Everolimus is a macrolide antibiotic that possesses the ability to suppress the immune response and cell proliferation leading to prevention of restenosis similar to sirolimus.[12] It possesses greater polarity than sirolimus and hence has better bioavailability and is rapidly absorbed on the arterial wall and attains peak concentration within few hours thereby offering better efficacy.[12] Experimental data have shown that orally administered everolimus inhibits in-stent neointimal formation and significantly promotes neointimal healing.[62] Evorolimus has been found to act at a later stage than the calcineurin inhibitor cyclosporin and tacrolimus.[63]

Biolimus A9 also known as umirolimus is a novel sirolimus derivative, which is specifically designed for stent applications. It exhibits immunosuppressive properties similar to sirolimus, but due to its lipophilic nature it is absorbed rapidly about 10 times faster than sirolimus or everolimus.[64] It can easily cross the cell membrane and achieve therapeutic effects in its target tissue when compared to sirolimus and hence leads to lesser systemic exposure.[65] In terms of potency, biolimus readily enters the membrane layer of smooth muscle cells and induces cell-cycle arrest at G0 phase.[66] Tacrolimus (FK506) is another 23-membered macrolide lactone, a calcineurin inhibitor employed as an immunosuppressive drug during organ transplantation to avoid rejection.[67] Unlike sirolimus it exerts its pharmacologic effect by inhibiting calcineurin, a calcium-dependent serine-threonine phosphatase that activates the T cells.[68] Novolimus, an active metabolite of sirolimus, is an mTOR inhibitor macrocyclic lactone, which has anti-proliferative and anti-inflammatory properties and has received a great deal of attention.[69] It has been basically used for drug eluting stent applications and has a well documented safety and efficacy profile.[70] Zotaroliums is a semi-synthetic rapamycin derivative, which has been especially developed for drug eluting stents using phosphorylcholine (PC) as carrier.[71] It is a distinct cytostatic drug, which has an inherent growth factor inhibitory effect as well as immunosuppressive nature.[72] Its exceptional lipophilic nature has an advantage over other sirolimus analogues, making it a better choice for drug eluting stents.[72] Abbott clinical trials PREFER, ENDEAVOUR and ZoMaxx carried out with Zotarolimus eluting stent (ZES) coated with PC has proved its safety and efficacy by reducing thrombus formation and restenosis incidence up to 2%.[72] The major drawback of ZES is its higher rate of late stent thrombosis.[73] Myolimus is a versatile rapamycin analogue with excellent anti-proliferative property, site-specific drug delivery and wide therapeutic index.[74] The Elixir clinical study using DESolve - a myolimus eluting bioresorbable coronary stent consisting of myolimus-loaded bioresorbable polymer coating, indicated significant success with good efficacy profile, lower incidence of restenosis and high radial strength.[75,76]

4.1.3. Paclitaxel

Paclitaxel is a type of taxane and a potent anti-proliferative agent used to treat breast and ovarian cancer.[77] It alters micro-tubular dynamics and stabilizes the microtubule assembly during the mitotic cycle. This interferes with vital cell processes like cell motility, mitosis, stimuli-responsive activation, secretory functions and signal transduction.[59] Being a lipophilic agent, the systemic levels of paclitaxel effectively inhibit the migration and proliferation of vascular smooth muscle cells.[78] High dose of paclitaxel has been shown to cause inflammatory cell loss, medial thinning and increased risk of stent thrombosis. Moderate doses of paclitaxel have been reported to elicit biocompatible responses, promote re-endothelialization and remodeling.[79] Low doses of paclitaxel completely inhibits growth, proliferation and migration of smooth muscle cells for an extended duration due to the structural alterations caused in the cytoskeleton.[78] Paclitaxel eluting stents and sirolimus eluting stents are considered to be the first generation of drug eluting stents.[80] Clinical trials TAXOL,

DELIVER-I, ELUTES and ASPECT conducted with paclitaxel-eluting stent exhibited dose-dependent reduction in restenosis and target-lesion revascularization but were also found to increase the sub-acute thrombosis.[59]

4.2. Anti-inflammatory drugs used in DES

4.2.1 Curcumin

Curcumin, a major polyphenol present in turmeric, has been used as a medicine in traditional Indian medicinal system due to its wound healing, anti-inflammatory as well as anti-oxidant properties.[81] Due to its wide range of actions, curcumin can play an inhibitory role on the growth of smooth muscle cells, reducing in-stent restenosis and enhancing endothelialization. Curcumin was shown to suppress the expression of leukocyte adhesion molecules such as intracellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin on endothelial cells induced by TNF-α. This has been postulated to occur through its ability to inhibit TNF-α-induced NF-κB activation.[82] Curcumin also inhibits collagen and adrenaline-induced aggregation of platelets.[83] Platelet aggregation triggered by collagen has been associated with an increase in the thromboxane level.[84] It is, therefore, likely that curcumin may have anti-thrombotic activity. Additionally, curcumin has been also been reported to block the action of arachidonic acid, platelet-activating factor and collagen thereby suppressing the aggregation of platelets triggered by epinephrine, ADP and collagen.[85]

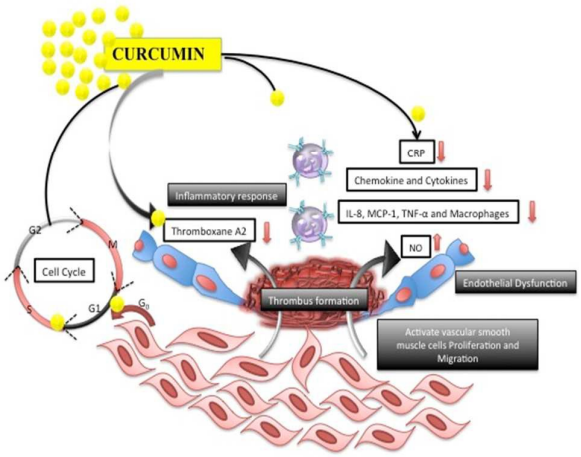

Figure 4. Shows main targets of Curcumin in vascular space. CRP: C-reactive protein, IL-8: Interleukin-8 MPC-1: monocyte chemoattractant protein-1, TNF-α: tumor necrotic factor alpha, NO: nitric oxide.

Various studies have reported that curcumin-eluting stents are highly thrombo-resistant and display dose dependent reduction in restenosis.[86,87,82] However, extensive clinical trials are required to establish the potential of curcumin-eluting stents in preventing stent-associated complications. **Figure 4** depicts the various molecular targets of curcumin in blood that are beneficial for its use in DES.

4.2.2 Resveratrol and Quercetin

Red wine contains numerous beneficial polyphenols with resveratrol and quercetin being the major components. Both these molecules have been recognized for their anti-inflammatory and anti-allergic response.[88] It has been established that platelet activation is the main cause of thrombosis in drug eluting stents. The potential mechanism behind platelet activation is through adenosine dinucleotide phosphate (ADP) as well as protein kinase C (PKC).[89] Resveratrol-loaded stents exhibited a tendency to inhibit platelet aggregation as well as P-selectin-positive platelets in a dose-dependent manner and subsequently reduced thrombus formation.[90] Additionally, both flavonoids have demonstrated anti-migratory and anti-proliferative actions on vascular smooth muscle cells (VSMCs).[91]

They have been found to inhibit activation of inflammatory cells and aid endothelial cell function.[92] Quercetin's anti-inflammatory effects may be partly due to its ability to inhibit inflammation-inducing enzymes cyclooxygenase (COX) and lipo-oxygenase (LOX), which in turn decreases the inflammatory mediators such as prostaglandins and leukotrienes.[93] Kleinedler *et al.,* demonstrated that polyphenols coated stents show reduction in neointimal hyperplasia, accelerate re-endothelization and also show a dose-dependent activation of platelets and macrophages.[94,95] **Table 2** lists other therapeutic molecules that are under active investigation for addressing stent-related complications.

Though different drugs have been investigated in DES, each drug has several drawbacks that have resulted in additional therapy-related complications in patients. The use of anti-proliferative agents to suppress SMC proliferation also retards endothelialization thereby enhancing the risk of thrombosis. Hence additional medication in the form of anti-thrombotic agents has to be administered routinely to the patient to reduce the risk of thrombosis. The prolonged use of such drugs leads to several side effects. Therefore, the possibility of shifting from single drug eluting stents to multiple drug eluting systems is being actively explored. However, the best combination of drugs that will not interfere with each other's action or cause undesirable adverse effects, while enhancing endothelialization and suppressing smooth muscle cell proliferation is yet to be established in a clinical setting.

Table 2. Other therapeutic molecules that have been employed in stent coatings for the treatment of cardiovascular diseases.

Therapeutic agent	Salient properties
Dexamethasone	Anti-inflammatory, immunosuppressive glucocorticoid, which inhibit cytokines, chemokines and other cell adhering molecules during fibrosis. It is also an anti-proliferative agent that inhibits vascular smooth muscle cell proliferation to lower the risk of restenosis.[96,97]
Phytoncide	A volatile plant extract with anti-oxidative, anti-inflammatory property. Studies also indicate its anti-thrombogenic nature.[98]
Emodin	A naturally existing anthraquinone derivative that inhibits TNF-α-induced proliferation, migration, and expression of matrix metalloproteins (MMP-2 and MMP-9) as well as inflammatory responses by vascular smooth muscle cells.[99]
Epigallocatechin Gallate	A catechin derivative that plays an important role in inhibiting protein tyrosine kinase activity and reduces the proliferative response of vascular smooth muscle cells. Galloyl group has hypolipidemic and anti-oxidant effect reduce the serum cholesterol level by inhibiting low-density lipoprotein (LDL) oxidation following the degradation of the oxidized-LDL by human monocyte-derived macrophages.[100]
Echinomycin	Anti-cancer agent, Possesses anti-thrombotic and anti-inflammatory properties and an effective response to vessel injury.[101]
Tamibarotene	Anti-thrombotic and endothelialization properties.[102]
Cytochalasin	Reversibly blocks actin polymerization and inhibits SMC contraction and geometric remodeling resulting in inhibition of restenosis.[103]
Leflunomide	Immunomodulatory molecule that suppress systemic inflammation with regard to cardiovascular disease along with significant reduction in the rate of MI. It inhibits the NFκB signaling pathway involved in both inflammation and atherogenesis. It also interfaces leukocyte-

	endothelial cell adhesion.[104]
Statins	Used to decrease cholesterol levels by inhibition of the enzyme HMG-CoA reductase. Demonstrates anti-coagulating activity by stimulating the protein C pathway.[105]

SMC: Smooth Muscle Cells, MI: Myocardial Infraction, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A.

5. Polymer choices for coating stents

Polymers have wide-ranging applications in the biomedical field, especially for fabrication of DES.[106] Polymer coatings have been used for entrapping a broad spectrum of therapeutic agents including drug molecules, proteins, peptides and nucleic acids [107] and enable their sustained release over an extended period of time. Polymer coatings for drug-eluting stents present a significant improvement in the overall clinical outcome and reduce the problems associated with bare metal stents. [108] The incidence of thrombosis and restenosis has reduced up to 50% with the drug eluting polymer coatings on the stent surface.[109] Both non-biodegradable and biodegradable polymers have been studied extensively for drug eluting stents. Non-biodegradable polymers are found to be non-reactive, bio-stable and give permanent support to lumen.[110] However, long exposure times associated with such coatings give rise to concerns over chronic foreign body inflammation that consequently results in intense proliferation of smooth muscle cells leading to in-stent restenosis.[111] Due to this shortcoming, biodegradable or bioabsorbable polymers have been explored as an alternate option for coating. **Table 3** described some of the biodegradable polymers used for stent coating. Their tuneable degradation and sustained drug release properties make them as a preferred coating material for stent applications.[112] As these coatings degrade into non-toxic products with time, they possess the advantage of not eliciting any long-term foreign body response in arteries.[113] These features of biodegradsable polymer are mainly dependent on their physicochemical properties such as molecular weight, crystallinity, molar ratio, hydrophobicity and glass transition temperature [114] Lower molecular weight polymers tend to degrade faster than higher molecular weight polymers, whereas the molar ratio of the monomers in a copolymer can affect its crystallinity and mechanical properties.[115,116] The other significant advantage of biodegradable polymer coatings is that they can serve as controlled drug delivery systems in order to attain sustained release of the drug.[2] In addition, a bioabsorbable polymer-coated stent will restore blood flow in the blocked artery and support the vessel similar to conventional stents. After a specific time interval, the coating gradually gets resorbed thereby reducing the possibility of long-term inflammatory response.

Table 3. List of biodegradable polymers used for stent application

Polymers	Characteristic Features
Poly(L-lactide-co-glycolic acid) (PLGA)	Biocompatible, tunable mechanical properties with controlled drug release.[117] Degradation can be modified to avoid long term polymer exposure.[118] **Drawback: Its poor flexibility can cause defects**
Poly D,L-lactic acid (PDLLA) and Poly L-lactic acid (PLLA)	PLLA has high tensile strength and toughness when compared to PDLLA [119,120] **Drawback: PDLLA degrades faster than PLLA**
Polycaprolactone (PCL)	Highly viscoelastic and superior rheological properties [121] **Drawback: Slow degradation rate and lower strength modulus**
Poly(L-lactide-co-caprolactone) (PLCL)	Copolymer integrates the properties of poly-L-lactide such as biocompatibility and higher degradation rate, and the characteristic mechanical properties of poly(caprolactone) such as flexibility.[122,123] Tuneable elasticity, Biodegradability, non-toxic nature of poly (lactide-co-caprolactone) make it promising for use in drug eluting stents.[124]

5.1. Hydrogels as stent coating materials

Hydrogels are emerging as a unique coating option for drug eluting stents due to their biocompatibility and biomimicking nature.[125] Natural polymers such as collagen, gelatin and polysaccharides as well as synthetic polymers like poly(ethylene oxide) and poly(vinyl alcohol) are the most common hydrogels investigated in the field of tissue engineering and drug delivery systems.[126,127] High water retention, anti-thrombogenic nature, tunable structure, stimuli sensitive features and drug diffusion properties are typical characteristics of hydrogels that have resulted in their widespread use as a biomaterial.[128] Hydrogels have been considered as good delivery systems for a diverse range of molecules such as therapeutic molecules, proteins, cells and growth factors, but their hydrophilic nature limits their ability to deliver lipophilic molecules.[129] Therefore, hydrogel composites have been designed to load nano and microcarriers in their 3D matrix for a higher encapsulation and controlled drug release.[130] Various studies indicate that chitosan, heparin-collagen and hyaluronic acid are the most promising hydrogel matrices for DES coating. These hydrogels are charged at physiological pH and hence can be easily assembled through layer-by-layer assembly on the stent to form multilayered hydrogel film encapsulating drug-loaded nanoparticles.[129,131] Coating methods such as dip- and spray coating followed by freeze drying or lyophilisation have been employed to bind hydrogels through hydrogen bond associations or non-covalent bonds to the stent surface.[132] But, the hydrogel attachment is not stable for long-term and hence new methods such as photo-crosslinking and free radical Fenton reactions have been explored to increase the stability of hydrogel coating.[133] However, the poor mechanical strength and fast degradation rate of hydrogel coatings limit their extensive application in DES.[128]

Surprisingly, a scan of literature reveals that the range of polymers investigated for stent coatings have been very limited and additional biodegradable systems that are biocompatible, hemocompatible with adequate mechanical strength and elasticity needs to be explored.

6. Smart alternatives to conventional polymer coating

6.1 Bioresorbable Stents

Metal stents remain in the coronary artery for the life time of the patient. Even in the absence of restenosis, a metal stent has the potential to prevent normal dilatation of coronary arteries in response to physiological conditions like exercise. The effect may be negligible when a short stent is used in a single vessel, but

when multivessel long stents are used, the coronary reserve can be affected. Long stents in major arteries like Left anterior descending (LAD) and posterior descending artery (PDA) can prevent the attachment of surgical grafts in the event of restenosis. This challenge has promoted the development of special polymers that can elute drugs to inhibit neointimal proliferation, provide radial strength to prevent acute vessel closure and disappear gradually leaving a normal vessel wall.

Poly-L-lactic acid (PLLA) scaffold is the World's first biodegradable stent and is made of high molecular weight PLLA. PLLA is most frequently used in current generation of bioabsorbable stents because of its key mechanical properties. It is a semi-crystalline polymer, which degrades *in vivo* predominantly through hydrolysis.[134] It has high elastic modulus, can withstand deformation and reduces the amount of recoil in the vessel.[135] After deployment of the polymeric absorbable stent, the polymer starts absorbing water from the surrounding tissue. With time, the stent loses mass as the polymer starts fragmenting into smaller lower molecular weight oligomers.[136] Due to its semi-crystalline nature, PLLA initially provides mechanical support while the amorphous segments facilitate a uniform dispersion of drug and serves as a controlled drug delivery system. A study performed using a porcine model has shown that stents coated with high molecular weight PLLA was well tolerated and effective.[137] The first absorbable stent that was implanted in humans is the poly L-lactic acid (PLL)-based Igaki-Tamai stent (Igaki Medical Planning Company, Kyoto, Japan). This stent underwent clinical trial in coronary artery disease, but further development and marketing was not carried out possibly due to vascular injuries report during trials.[138] Other PLLA based BRS (Bioresorbable scaffold) which are under clinical trials is Abbott Vascular and DeSolve BRS. The BRS (Bioresorbable Scaffold) everolimus-eluting stent manufactured by Abbott Vascular, Santa Clara, California, is the first in the category of bioabsorbable stents that was found to possess similarities with the metallic drug eluting stent in its clinical outcome (ABSORB Cohart A and ABSORB Cohart B study) two years post-implantation. In addition, this stent exhibited more beneficial outcomes due to full-stent absorption. The BVS eluting stent comprises a coating of everolimus-entrapped poly(D,L-lactide) over a bioabsorbable PLLA backbone. BVS has reached the market and thousands of stents have been deployed in Europe and Asia and is awaiting FDA approval in USA.[138] Another revolutionary bio-absorbable scaffold is the Elixir Medical Novolimus-eluting bioresorbable coronary stent scaffold system**.** It involves a PLLA based scaffold coated with polymer drug matrix that takes about a year to degrade.[139] The degradation time was chosen based on earlier studies where it was found that it takes approximately a year to restore the patient's coronary vessel eventually to its normal *de novo* state. The stent scaffolds have the capability to retain the radial strength, support the blood vessel during the vessel-healing period apart from possessing significant expandability and degradability. In cases of ineffective contact between the stent strut and the arterial wall, the stent scaffolds have been found to self appose to the vessel wall of nominal sizes. [138,140]

Bioabsorbable magnesium stents: The modern trend in stenting technology is the development of short-term implants composed of biocompatible and fully degradable materials, which reinforce the vessel at the time of recoil followed by their complete degradation.[141] Such degradable implants offer better healing and reformation of local vasculature with positive remodeling.[142] Bioabsorbable magnesium stents are the first generation bioabsorbable metal alloys that were developed to overcome the limitations imposed by bare metal stents such as late in-stent restenosis, inflammation, late stent thrombosis, prolonged antiplatelet therapy and low radiopacity.[143] Magnesium stent exhibits a controlled biodegradation and is generally absorbed within the body in two months.[144] In addition, magnesium stents are also magnetic resonance compatible and are radiolucent.[135]

Magnesium alloys were previously used in biodegradable orthopedic implants.[145] Magnesium stents have low elastic recoil when compared to stainless steel stents.[145] Their ultimate tensile strength is around 250 MPa.[16] They are hypo-thrombogenic at the time of degradation thus making them a promising candidate for coronary stent applications.[146] The stent is constructed with a magnesium alloy (WE43) and also contains a small percentage of zirconium, yttrium and rare earth metals.[2] The stent is fabricated from a single tube of an absorbable magnesium alloy using a laser beam.[147] These bioresorbable metallic stents display controlled erosion and possess additional benefits of anti-thrombotic, anti-arrhythmic and anti-proliferative properties.[148] Since magnesium is the fourth most important micronutrient in the biological system, local toxicity of the degradation products of these stents is unlikely.[149] Surprisingly, this stent system failed in the clinical trials with unacceptable rates of restenosis (45%) and poor radio opacity and radial strength.[150]

6.2. Polymer-free drug eluting stents

Due to concerns arising on the safety of the polymer coating used for an extended duration, development of a theoretically safer "no-polymer" strategy for drug delivery has gained momentum in recent years.[53,54] It has been suggested that the degradation products of biodegradable polymers and the presence of unreacted monomers in the polymer may lead to the induction of the inflammatory cascade.[151] In an effort to avoid polymer coating, the surface of the drug eluting stents have been designed to be porous to serve as reservoirs for the sustained release of the anti-restenotic agents. This strategy enables accomplishment of "programmable" drug elution without the use of polymers.[53,54] A typical polymer-free DES comprises a microporous or nanoporous surface finishing on a 316L stainless steel stent. This design enables direct drug adhesion to the stent surface and facilitates polymer-free drug-delivery.[152] In another method, multiple micro-reservoirs loaded with anti-proliferative drugs were incorporated into the abluminal side of the stent and this design ensures drug delivery to the abluminal-side only.[152] To incorporate thrombo-resistance, a high density ultrathin pyrolytic carbon film coating of high density was made on the stent surface. This coating has been suggested to be more biocompatible.[152]

7. Evolution of endothelialization strategies

The major drawback of using anti-proliferative drugs is delayed re-endothelialization, which results in increased risk of thrombosis and disturbs the vascular space. Hence, innovative attempts to promote endothelialization have been made in the recent years. Though many of these strategies are currently in the laboratory and pre-clinical stages only, it is expected that some of them may progress to clinical trials soon.

7.1. Endothelial progenitor cells (EPC) Capturing therapy

Endothelial progenitor cells and nitric oxide-based strategies aim to address the re-endothelialisation related complications and also expand the therapeutic options for treatment of Coronary artery disease. This stent coating enables a cell-based therapy by capturing the circulating endothelial progenitor cells and/or employs biopharmaceuticals such as proteins, peptides, monoclonal antibodies and nucleic acids to modulate nitric oxide synthesis thereby promoting endothelialisation on the stent surface.[153]

Antibody therapy is a unique and effective way to repair the vascular injury by targeting circulating endothelial progenitor cell to the stent surface. Endothelial progenitor cells (EPC) have specific surface markers such as CD34, CD31, CD105, CD133 and CD144, which play a key role in endothelium lining.[154] The key concept in this therapy is to covalently immobilize monoclonal antibodies of endothelial cell markers on the stent surface through polymeric carriers such as hyaluronan-chitosan, poly L-

lactic acid (PLLA), which can capture the circulating endothelial progenitor cells and facilitate re-endothelialisation on the stented area.[155] (**Figure 5**) The most extensively used antibodies are anti-CD34, anti-CD133, CD144 and anti-CD105. Purified mouse anti-CD34 monoclonal antibody has been found to display specific interaction with the human CD34 antigen present in hematopoietic precursor cells and endothelial cells.[156] Experiments carried out with mouse anti-CD34 monoclonal antibody revealed that they do not react with normal peripheral lymphocytes, monocytes, erythrocytes, granulocytes, or platelets.[156] Human Vascular Endothelial (VE)-cadherin also known as CD144, is a typical endothelial cells marker found in veins, arteries, capillary and large vessels and is found localized at the cell-cell junctions. They are reported to play a key role in angiogenesis and in endothelial cell biology by regulating the cohesion and also the organization of the intercellular junctions.[157] Antibodies against specific types of cadherins have also been attempted to recruit endothelial cells at the stent surface for re-endothelialization.[158] A recent attempt reports the development of a 'dual therapy stent' also known as Combo stent (OrbusNeich), which essentially comprises of a combination of abluminal sirolimus eluting polymer coated-stent along with an antibody that attracts endothelial progenitor cells to address the challenges of delayed coronary artery healing associated with drug eluting stents.[159] Antibodies against CD34 were employed to demonstrate the superiority of this stent over conventional sirolimus eluting stents.

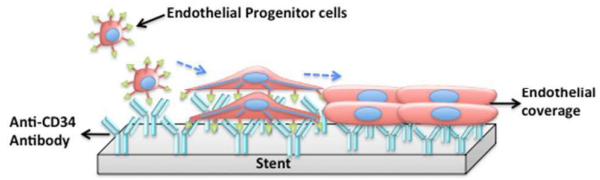

Figure 5. Depicts the schematic representation of antibody therapy.

Stem cell therapy is a promising strategy to re-endothelialize stents with rapid endothelial cell (EC) adhesion and proliferation by using exogenous stem cells. [160,161] This therapy uses various isolated cells such as cardiac stem cells, mesenchymal stem cells, umbilical cord blood cells and endothelial progenitor cells to coat stent. [162] The EPCs coated stent can either differentiate into endothelial cells or stimulate the migration of neighboring endothelial cells (ECs) or enable direct capture of the circulating endothelial cells (CEC) from the blood stream, which stimulate re-endothelialization of the inner lining of the stented blood vessel.[163] However, ethical issues involving stem cells have limited progress in the development of stem cell based stenting techniques.

In situ endothelialization was attempted through specific binding of endothelial cells on the stent surface using the EC-specific peptide sequence Arg-Glu-Asp-Val (REDV) immobilized on the polymer layer of the stent.[159] However, clinical trials revealed that this strategy did not effectively prevent in-stent restenosis (ISR). This setback highlights the fact that *in situ* endothelialization on the stent surface involves more complex factors than endothelial seeding alone and additional parameters to curtail restenosis need to be introduced.

Other biomolecules investigated to improve endothelialization include the metabolic intermediate sphingosine-1-phosphate [164], organoselenium compounds such as 3,3'-dipropionicdiselenide (SeDPA) and selenocystamine.[165] These molecules induce the production of nitric oxide through the catalytic activity of endogenous S-nitrosothiols present in the blood [166] as well as by stimulating growth factors like VEGF (vascular endothelial growth factor) and bFGF[167] (basic fibroblast growth factor).

Most of the reports on antibody and stem cell therapies have employed stainless steel stents for coatings.

7.2. Gene Therapy

An emerging paradigm in stent technology is the evolution of gene eluting stents (GES) to overcome the shortcomings of DES and stent-related complications. Gene therapy is an efficient therapeutic approach to address the disease processes leading to the vascular injury by focusing both on the structural and biological basis of restenosis and other molecular level complications.[168] It employs therapeutic genes for growth factors and cytokines that are specific to their molecular targets, which could be used to treat in-stent restenosis and late-stent thrombosis.[169] **Figure 6** summarizes the different classes of GES based on the type of vectors, coating, immobilization methods and therapeutic genes employed.

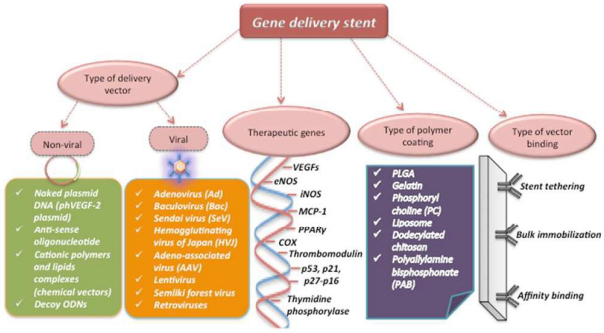

Figure 6. Pictorial presentations of classes of GES (gene eluting stent). VEGFs: vascular endothelial growth factors, eNOS: endothelial nitric oxide synthase, iNOS: inducible nitric oxide synthase, MCP-1: monocyte chemo attractant protein, PPARγ: peroxisome proliferative activity gamma, COX: cyclooxygenase.

A typical gene eluting stent consists of a permanent stent metal platform, a properly sequenced therapeutic gene product specific to a specific molecular target, a safe and potent gene delivery system and a coating to immobilize the vector on the stent.[170] For delivery, both viral and non-viral gene delivery systems have been explored in the development of effective gene eluting stents. (**Figure 7)** Cationic non-viral delivery systems formulated from cationic polymers and cationic lipids have been complex with plasmid DNA or small interference RNA (*si*-RNA).[171] Decoy oligonucleotides, which are short 10 base pair oligonucleotides, act as a regulator for the expression of target gene and have been reported to protect the therapeutic gene from the degradative enzymes.[172] The therapeutic efficacy of the non-viral gene delivery systems are not very high and hence attempts to employ viral vectors for the release of the therapeutic genes have also been documented in literature. Retroviruses such as Semliki forest viruses,[173] Sendai viruses,[174] baculoviruses,[175] hemagglutinating viruses,[171] lentiviruses,[176] and adeno-associated viruses,[161,176] have been employed for the delivery of therapeutic genes from the stent. A range of polymers had been used in gene eluting stents for immobilizing the therapeutic genes. These include the biodegradable poly (L-lactide-co-glycolide),[171] gelatin,[177] phosphatidyl choline,[178] docecylated chitosan,[179] poly (allyl aminebisphosphonate)[180] and liposomal vesicles.[181] The immobilization of the therapeutic genes and their vectors with the stent have been accomplished through affinity binding techniques[182] or through stent tethering[182] or using bulk immobilization strategies.[182]

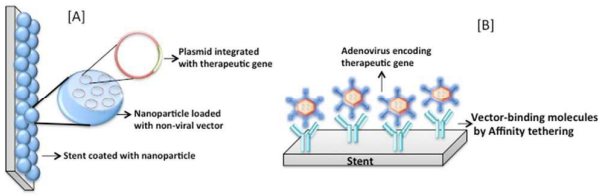

Figure 7. Illustrates the detail of the two types of delivery systems, non-viral [A] and viral vector [B] stents for therapeutic gene delivery.

Different types of therapeutic genes have been employed in stents. These include genes encoding for vascular endothelial growth factor (VEGF),[183] endothelial nitric oxide synthase (eNOS),[168] inducible nitric oxide synthase (iNOS),[180] monocyte chemotactic protein (MCP-1),[184] peroxisome proliferative activated receptor (PPAR-□),[185] cyclooxygenase (Cox),[186] thrombomodulin,[187] p53,[188] p21, p27 and p16,[189] and thymidine phosphorylase.[190] Genes encoding for regulatory proteins such as thymidine kinase and cytosine deaminase, which impair cell cycle

during the S phase of the cell cycle, have been employed in GES.[191] GES with cytosine deaminase gene have exhibited higher apoptosis levels of vascular smooth muscle cells and enhanced inhibition of neointimal formation.[192] Recent strategies have employed vascular gene therapy that simultaneously targeted multiple pathways resulting in pleiotropic effects that accelerated re-endothelialization apart from decreasing intimal hyperplasia.[193] Several groups have investigated the therapeutic potential of vascular endothelial growth factors (VEGFs) for enhanced anatomical and functional recovery of the endothelium post-injury. Some of the studies have employed a naked plasmid DNA encoding for a 165-amino acid isoform of VEGF (phVEGF165).[194] Nitric oxide (NO) is another pleiotropic agent that is produced in the blood vessels by nitric oxide synthases (NOS). NO is considered to be an important molecule as it performs diverse functions that include inhibition of platelet activation apart from proliferation and migration of vascular smooth muscle cells (VSMC), prevention of leukocyte chemotaxis, triggering VSMC apoptosis, vasodilation and re-endothelialization.[195] These therapeutic genes are always accompanied with the co-delivery of a reporter gene that serves as a selectable marker to the vascular tissue.[170] The use of GES embodies an attractive mechanism for delivery of therapeutic gene to the site of the atherosclerotic blood vessel with the following advantages: (i) enables targeted therapy at the pathophysiological site; (ii) enhances local concentration of the therapeutic gene at the target site due to immobilization of the vector to the stent struts resulting in reduced risk of systemic toxicity and enhanced transfection potential at the targeted site; (iii) combines revascularization with gene delivery in a single standard procedure; (iv) stents can facilitate extended vector release and (v) stent-conjugated vectors are able to withstand the shearing force due to blood flow and hence exhibit better therapeutic outcomes.[170]

However, using stent as a platform for gene delivery poses several challenges. These include delivery issues of the therapeutic gene to the target site that still remains to be optimized, stent efficiency, biocompatibility of coatings, surface modification for viral vectors to reduce immunogenicity, complex vector immobilization techniques and inadequate delivery systems for feasible vector to achieve optimized gene expression and potency.[196] Nevertheless, this concept holds much promise for therapeutic interventions in the near future.

8. Recent advances in Stent Technology

Stent technology has incorporated frequently evolving concepts in the field of interventional cardiology that have served to advance the treatment for cardiovascular diseases. The bare metallic stent has gradually transformed into drug eluting stents that have also undergone a radical change from first generation to third generation drug-eluting stents. However, the present types of drug-eluting stents still suffer from complications arising from re-narrowing of the stented blood vessels in high-risk patients and occurrence of late in-stent thrombosis due to premature discontinuation of dual anti-platelet therapy that is prescribed to stented patients and other clinical consequences.[197] Therefore the need of the hour is integration of ideal stent design, perfect choice of materials and drug molecules based on the underlying pathology of disease complications, to obtain a more efficacious and safer drug eluting stent. Development of newer stents with very low rates of restenosis and stent thrombosis are further limited by high cost and invasiveness. In the following sections, we have described some of the latest stratagems that have emerged in drug eluting stents with special emphasis on the unique advancements achieved through the incorporation of nano-dimensional features on stents.

8.1. Nanotechnology-enabled stenting strategies

Nanotechnology is a promising strategy that has improved the quality of both conventional therapy and diagnosis. The use of nano-dimensional carriers loaded with drugs has been found to improve the drug solubility, stability, bioavailability, reduce immune recognition, facilitate regulated drug release and most importantly ensure site-specific delivery of the drug.[198] Numerous examples of nano-dimensional drug delivery systems are available in literature. These include nanocrystals, vesicles, micelles, nanoparticle-drug conjugates, magnetic nanoparticles, nanogels and biodegradable nanoparticles.[198] Nanocarriers have also enabled use of uncommon routes of drug administration for better therapeutic outcomes.[199] Nanoparticles can be surface modified to avoid immune recognition and can be used to bind to specific receptors on the cell surface thereby enabling targeting of specific tissues, cells, organelles, receptors and hence has been extensively explored for drug, gene and vaccine delivery applications.[171] Nanoporous membranes have also been reported for controlled-delivery drug devices.[199] Eliciting specific responses from cells through manipulation of the scaffold topography through incorporation of nano-dimensional features on the surface or through peptide sequences that bind to specific cell surface receptors has also been extensively investigated.[200] Integration of such nano-interventions in stents have also been attempted to address complications arising due to conventional stents. The following section highlights some of the nanotechnology-mediated stent concepts.

8.1.1. Nanofiber-coated stents

During stent deployment, the polymer coating on the drug eluting stent tends to crack and delaminate due to poor mechanical properties and weak adherence on the metal. To avoid such defects, a semi-permeable membrane with minimal imperfections and good physico-mechanical properties can be a good substitute for therapeutic carriers.[201] Nanofibers are an appropriate choice to form a therapeutic membrane on stents with flexible surface, high loading capacity as a result of its large surface area-to-volume ratio and can provide an additional reinforcement for the vessel wall.[202] A nanofibrous membrane consists of uniform nano-dimensional fibers, which are aligned directly on the abluminal side of stent. These nanofibers can be easily fabricated by electrospinning. [203] As a delivery system, it can be used to encapsulate drugs, peptides, growth factors or stem cell by using loading techniques like co-axial electrospinning, surface coating, blending and core-shell electrospinning. [204] Such systems can minimize frequent loss of therapeutic agent in bloodstream as well as act as a barrier between the stent and vessel wall.[205] The delivery mechanisms operational in nanofibrous membranes can be diffusion or polymer degradation-based depending on the choice of the polymer used for fabricating the nanofibrous membrane. [206] The high surface area to volume ratio of the nanofibers and their microporous structure favours endothelial cell proliferation and migration, which are highly desirable in drug eluting stents.[207] The nanofiber-coated stents also provide uniform laminar flow throughout the blood vessel, which is a principal requirement of a drug eluting stent.[208] It has been demonstrated that coating of hormone-loaded nanofibers of PLGA and PLA on the stent surface offered superior coating stability and a high endothelial proliferation rate suggesting that such strategies may soon replace existing concepts in stent design. Concerted efforts to identify the appropriate material from which the nanofibers will be fabricated are required to transform this concept from bench to bedside.[208] Studies have demonstrated the successful use of nanofiber-coated non-vascular stent for tracheal regeneration, treatment of benign cardiac stricture and in an esophageal stent for treatment of cancer. [209,210]

8.1.2. Nano-textured stents

Nanotexturing is a nanotechnology-based approach to improve

the surface property of stent, which can enhance its cell interaction. It also enables efficient drug delivery and reduces the polymer content.[211] It is a cost effective process leading to the formation of a uniform nano-porous structure on the abluminal surface of the stent with the help of pulsed laser.[212] As a result, the surface to volume ratio of the drug eluting stent will significantly increase their drug-loading capacity [213] and also such surface modification promote cell adhesion via contact guidance by the nano-patterns [214] Laser based nanofabrication is the most common and successful method for fabricating nanotextured drug delivery system on the stent surface due to their controlled and flexible micro-and nano-patterning capability.[212] Other methods include photolithography, x-ray and electron beam lithography, colloidal and electrostatic assembly, self-assembly, sol gel process and electrochemical modification such as anodic oxidation.[213,215] Femtosecond laser patterning and plasmonics are other techniques that have been reported for nanotexturing vascular stents. These are simple and inexpensive methods causing less thermal damage. [216,217,212] Ultra short laser pulses upon interaction with the stent surface generate a non-equilibrium state of matter to cause ablation. By varying the amplitude and other experimental parameters, different sizes and shapes can be patterned on the surface. [212,218] Various surface topographies like dimples, cones, pores, rods, spikes and spheres can be created through nanofabrication.[218] *In vitro* release studies have confirmed that the increased surface area of the nanotextured stent enables three times greater retention of drug molecules when compared to its untextured counterpart. [212]

8.1.3. Nanotube coating

Among the various nanotexturing structures, nanotubes proved to be most efficacious drug delivery systems due to their immense drug loading capability and large surface area to entrap multiple molecules for a sustained drug release and controlled degradation.[219] A typical nanotube-coating consists of hollow cylindrical nanostructures with uniform dimension, made up of both organic and inorganic materials such as polymer, lipid, carbon, silica, and metal oxides.[219] Carbon nanotubes, alumina and titanium dioxide nanotubes are most widely studied as drug eluting stent coating when compared to other materials. This is chiefly due to their easy synthesis, nano-porous nature, prolonged drug release properties and biocompatibility.[220] Electrochemical anodization and capillary driven assembly of nanotubes are the main methods that have been employed to fabricate nanotubes on stent substrates.[221,222] Furthermore, tailoring the dimensions such as thickness, length and diameter of the nanotubes enables controlled release of the drugs.[223] Various studies have been performed with nanotube coated stents. These include nanoporous anodic aluminium oxide (AAO), single walled carbon nanotube and anodized titanium oxide nanotube array. These coatings have been proved to be biocompatible and can effectively serve as a controlled drug delivery system [224-227] However, such coatings have also been reported to induce vascular inflammation and toxicity apart from concerns on their robustness and stability of the coating.[228,229]

8.1.4. Nanoparticle coating

Nanoparticulate delivery system is an emerging paradigm in stent technology for coating the stent surface.[171,230] Nanoparticles are nano-dimensional spherical carriers with high loading capacity, uniform distribution and possess fast permeability in vascular space. [231] As a local delivery system they are the most studied systems due to their permeability in biological systems.[232] Materials that can be used as nanoparticulate carrier systems include metallic nanoparticles (gold and silver), mesoporous silica and polymeric nanoparticles such as dendrimers, micelles (liposomes and block copolymer) [233] For stent coatings, polymeric nanoparticles have been extensively explored for therapeutic delivery due to their biocompatibility, sustained release properties and easy delivery of hydrophilic and hydrophobic

molecules.[170] Nanoparticles encapsulating therapeutic agents can be immobilized on the stent surface using spray, dip coating or by other methods such as cationic electrodeposition.[234,170] Studies have shown that the nanoparticle layer is regularly distributed on the stent surface without any voids giving a uniform surface and thickness, which can be regulated by controlling the deposition parameters.[235] Besides enabling targeted drug delivery at the diseased site, these nanoparticle-coated stents possess a therapeutic potential for the treatment of coronary artery disease by ensuring negligible focal inflammation. [171,230] However, this concept is still in its infancy and further in-depth studies are required to establish this as an effective stratagem.[236]

8.1.5. Magnetic nanoparticle-based coatings

Magnetic nanoparticles have emerged as an "on-demand approach" for highly controlled drug delivery. [237] These nanoparticles consist of magnetic elements which exhibit superparamagnetism such as iron, cobalt and nickel and their derivatives [238] Under an external magnetic field gradient, they release the therapeutic agents for site-specific and stimuli-responsive therapy [239] Such systems have also been explored in stent technology in recent years. An *in vitro* study conducted by B. Polyak and M. Chorny clearly indicated the biocompatibility of magnetic nanoparticle coating on the stent surface under a homogenous magnetic field [240,241] Biophan technology has developed novel magnetic nanoparticle-based stenting technologies that provide a higher degree of controlled and targeted drug delivery.[242] Nanomagnetic drug eluting stents represent a radical shift from the current passive approach in drug eluting stents to an active drug delivery system that releases specified amounts of the drug in response to an external electromagnetic stimulus.[241] This gives the opportunity to control the release of the anti-proliferative drug, constant release of which in the later stages is a potential reason of late-stent thrombosis. Magnetic mesoporous nanocomposite has also been recently explored as stent coatings due to their high surface area, porous nature, biocompatibility and better endothelialzation.[228] Yet another exciting application for this technology is that nanoparticles can be tuned to respond selectively to different wavelengths, thus enabling multiple drugs to be delivered at different times, controlled by unique electromagnetic signals. This multiple drug coating can be used to treat different complications simultaneously with specific electromagnetic signals for each drug.[242] However, this concept is yet to be validated through experiments. **Figure 8** depicts the various nanotechnology-enable concepts in stents that have evolved in recent years.

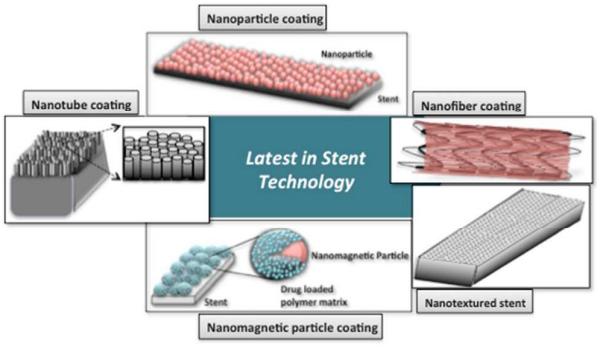

Figure 8. Emerging nanotechnology enabled-stent strategies.

It is evident from the above discussion that stents have evolved from being mere structural supports to functional materials that can aid better healing of the diseased region. However, though newer strategies have been developed for stent-based interventions, these have also given rise to new complications that need to be addressed. It is heartening to note that the novel stenting options have resulted in better survival and clinical outcomes than their predecessors. But further efforts are required to mitigate some of the complications associated with these modern stents. **Figure 9** depicts the evolution of stenting technologies over the decades along with their associated complications.

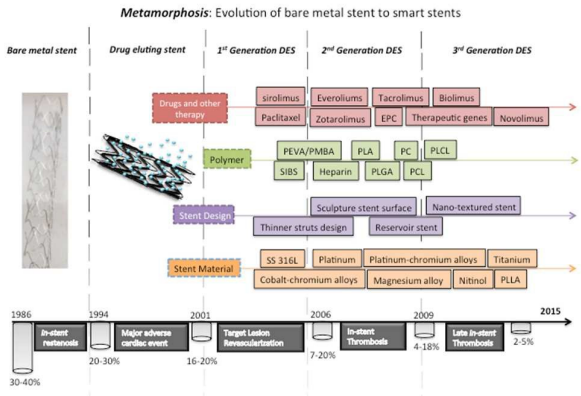

Figure 9. Pictorial presentation of stent evolution. DES: Drug eluting stent, EPC: Endothelial progenitor cells, PEVA/PMBA: polyethylene-co-vinyl acetate/poly-n-butyl methacrylate, PC: phosphorylcholine, SIBS: Poly (styrene-b-isobutylene-b-styrene), PLA: poly lactic acid, PLGA: poly(lactic-co-glycolic acid), PCL: Polycaprolactone, PLLA: poly L-lactide acid.

Conclusions

The evolution of stent technology was marred by the occurrence of restenosis in bare metal stents. Drug eluting stents solved the problem of restenosis, but at the cost of increased risk of stent thrombosis. The dual issues of stenosis due to intimal proliferation and stent thrombosis due to delayed endothelialisation, remains the Achilles heel of this form of interventional therapy. Stents have evolved from being mere supporting frameworks to multi-functional devices that also attenuate the complications arising due to stent deployment. Novel strategies in metallurgy, instrumentation, drug molecules and polymer technology has made stents thinner, stronger and polymer free, to enhance endothelialization while inhibiting smooth cell proliferation. Exciting new stents like immunostents and gene eluting stents are undergoing preclinical testing with promising results. A wider repertoire of stent materials, polymers and therapeutic molecules has catalyzed the development of the next generation stents that promise longevity, better therapeutic efficacy and lesser post-implantation complications. Nanotechnology-enabled interventions promise to further improve the stent performances though more in-depth studies and clinical trials are required in this direction to evaluate their efficacy. Coating techniques employed to modify the stent surface with polymer and drugs also can influence the stent performance. Thus identifying the ideal combination of material, therapeutic molecules, stent design and fabrication method is the need of the hour to establish the supremacy of stents for treatment of cardiovascular disorders.

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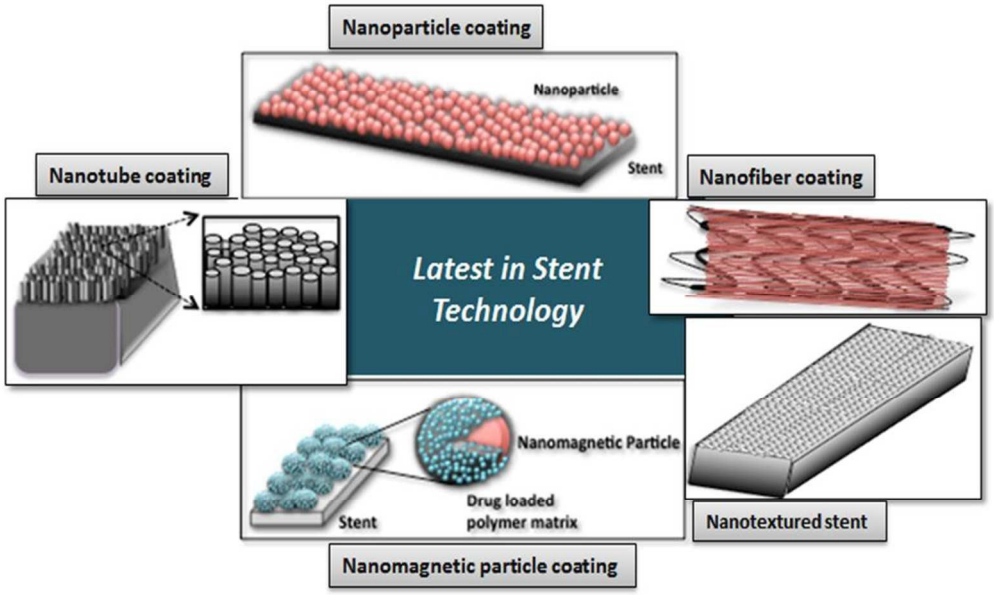

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