

# Drug Eluting Stents

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A REVIEW

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# Drug Eluting Stents: A Review

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## Abstract:

The introduction of stents has been a major advance in the treatment of coronary artery disease ever since the introduction of balloon angioplasty. The development of drug-eluting stents (DES) contributes a considerable breakthrough to Interventional Cardiology. By incorporating an anti-proliferative agent onto the surface of the stent, neointimal hyperplasia occurring within the stent, which is proved to be the main cause of in-stent restenosis (ISR), is markedly reduced. Stents coated with agents, like sirolimus or paclitaxel, when compared to bare metal stents (BMS), had shown a remarkable reduction in restenosis and target vessel revascularization (TVR) rates in large randomized clinical trials. However, because of the long-term incremental risks, benefits, and costs, drug-eluting stents have not yet been optimally evaluated in a broad spectrum of the patient. This article aims to provide a detailed review of Drug-eluting stents and summarize the recent progress in the treatment of coronary artery disease (CAD) as well as compare and update the results of clinical trials.

**Keywords:** Drug-eluting stents, in-stent restenosis, revascularization, thrombosis, percutaneous transluminal coronary angioplasty.

## Introduction:

The circulatory system is one of the most important organ systems of the human body. The heart being the main unit of the circulatory system depends on the coronary arteries for the blood supply to cardiac muscles. When the blood supply to the heart muscles is hindered, the resulting disease is said to be coronary artery disease (CAD). CAD is the most common type of heart disease and is the leading cause of death worldwide. According to world health organization (WHO), Cardiovascular diseases (CVDs) are the number one cause of death globally. An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Among these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke [1]. CAD can be treated with various methods, but the most effective and ultimate method of treatment over the years has been coronary angioplasty followed by a permanent placement of coronary stents. Balloon angioplasty was first applied to the revascularization of the femoral, popliteal, and renal arteries, and was adapted to the coronary arteries in the late 1970s [2]. But, it had several limitations including the risk of uncontrolled plaque formation and incidence of restenosis after revascularization. The use of coronary stents in the treatment of CAD had similar limitations like sudden occlusion of blood vessels due to thrombus formation on the stent and re-narrowing of the arteries [3]. Therefore, the major problem with percutaneous coronary intervention (PCI) and coronary bare metal stenting is the need for repeating the target vessel revascularization (TVR) due to restenosis. The restenosis rates with bare metal stents (BMS) were reported to be between 16% and 44%, with higher rates of stenosis attributable to several risk factors, in particular, the long lesion length and small vessel caliber [4]. Many drugs and medications were implicated in patients post PCI but in most cases, it failed to avoid restenosis. Thus, the need for a better and advanced treatment techniques to eliminate the repetition of revascularization was very high. Ultimately, to address the problem of restenosis a new type of stent was developed called a Drug-Eluting Stents.

Drug eluting stents are nothing, but the bare metal stents coated with a suitable polymer. The polymers coated are designed in such a way that they gradually release a drug to inhibit the cell proliferation that

causes restenosis. By the time all the drug has been released from the polymer, a period of between six and nine months – the main risk of restenosis has been minimized [5]. There is a steadily increasing body of clinical data comparing individual DES both with their BMS equivalents and with each other. It is evident that DES significantly reduce the incidence of restenosis compared with BMS, to levels of under 10 percent [6]. Thus, DES was considered as one of the greatest advancements in the field of Interventional cardiology. In this article, we provide a complete review of the evolution of stents, their types, in-stent restenosis (IST) pathophysiology, properties and benefits of DES, the effect of DES on the hyperplasia and summarization of various clinical trials.

### **Evolution of stents:**

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The first coronary angioplasty known as percutaneous transluminal coronary angioplasty (PTCA) was introduced in the late 1970s as a minimally invasive means of re-opening coronary arteries that had narrowed with plaque formation. However, this procedure soon became apparent that balloon angioplasty had its limitations. In numerous cases, the process weakened the artery wall to such an extent that although it is successfully dilated, the artery collapsed once the balloon is deflated, leading to the need for emergency bypass graft surgery (CABG), which increased treatment cost and unnecessary risks [7]. Various atherectomy techniques such as rotational atherectomy (rot ablation), Excimer Laser Coronary Angioplasty (ELCA), and Directional Coronary Atherectomy (DCA) were developed in the late 1980s and early 1990s, but these devices did not significantly improve the long-term outcome due to a lack of an impact on restenosis rate [8].

Bare Metal Stents (BMS) were the next big thing in the field of cardiovascular devices when it was introduced. Puel and Sigwart, in 1986, deployed the first coronary stent to act as a scaffold, thus preventing vessel closure during PTCA [9]. BMS has reduced the incidence of angiographic restenosis, which had an occurrence rate of 30-40%. By 1999, stenting composed about 84.2% of all PCIs. Despite the widespread use of these devices, bare metal stents had been associated with a 20-30% restenosis rate requiring reintervention [10]. In addition to restenosis, PTCA and BMS implantation caused exaggerated endothelial injury and inflammation, rendering both the stent and vessel highly thrombogenic. A fibrinogen layer covers the stent surface, further inducing platelet activation and thrombosis [11]. Further, when the use of BMS was expanded, especially in the high-risk restenosis groups of patients, such as those with small vessels, long and bifurcation lesions, and diabetes mellitus, ISR, and TVR escalated to the range of 50%–60% and 30%–50%, respectively [12]. In the late 1990s, extensive research was carried out to seek a solution to the problem of ISR. Brachytherapy with an insertion of radioactive devices in the coronary artery was initially developed to prevent ISR. Despite its moderate success, brachytherapy had limitations such as late thrombosis, geographic mismatch, relatively high cost, and requirement of radiation oncologists, which made it unsuitable for widespread and routine clinical practice.

In 2001, drug-eluting stents (DES) were introduced as a strategy to minimize restenosis and overcome the limitations of bare metal stents. The currently available polymer-coated stents contain antiproliferative agents which elute locally in the implanted coronary artery to prevent neointimal hyperplasia. The first DES to be launched was the Cypher® stent in 2003, followed by the Taxus® stent in 2004. Apart from physical differences in the design of the stent such as type of metal used; strut thickness; mechanics of strut interlinkage, the differences between the variety of DES currently available relate to the actual anti-restenosis drug used and the release characteristics of the polymer which indicates the amount of drug released and the time of occurrence [13]. 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. Thus, the rise of Drug eluting stents in the field of interventional cardiology. The generations of DES will be further discussed in this article.

## Types of Drug-eluting Stents:

Ever since the introduction of DES in the year 2001, it has undergone many changes with respect to structure and the coating materials used. First-generation drug-eluting stents, which used sirolimus or paclitaxel as drugs to fight restenosis, were shown to be superior to bare-metal stents and to balloon angioplasty in reducing the magnitude of neointimal proliferation, the incidence of clinical restenosis, and the need for reintervention.

Moving on, second or third-generation drug-eluting stents were designed to provide better stent deployment, safety, and efficacy. They differed from the first-generation stents with respect to the antiproliferative agent, the polymer layer, which acts as a reservoir for controlled drug delivery, and the stent frame. Improvements in stent structure may result in better stent apposition to the vessel wall, improved endothelialization and reduced platelet aggregation and thrombus formation, thereby reducing the incidence of stent thrombosis [13].

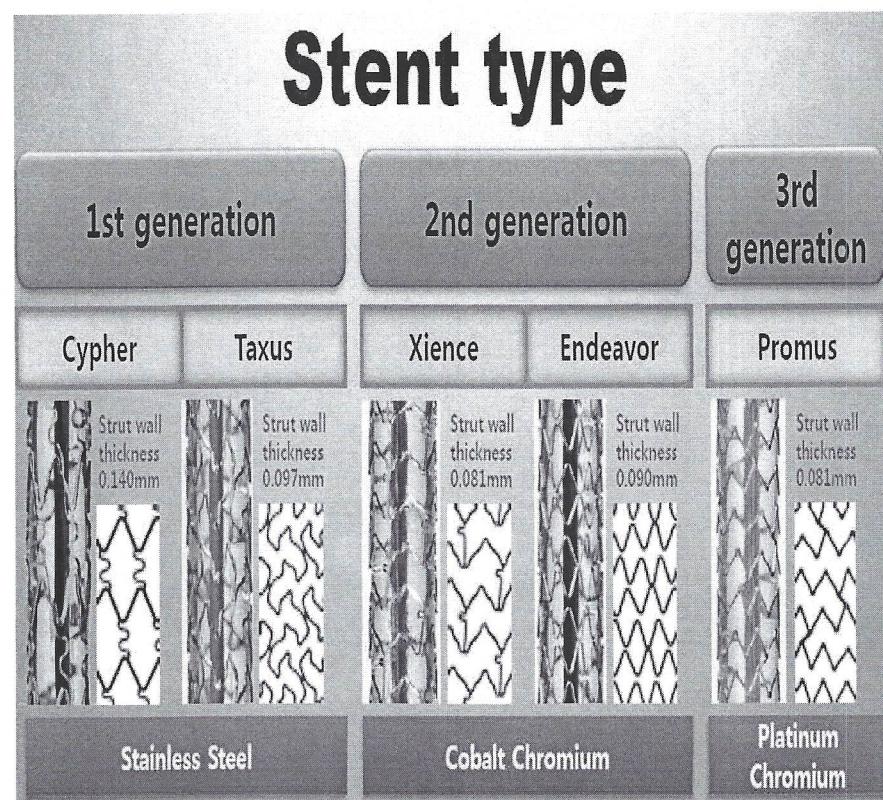


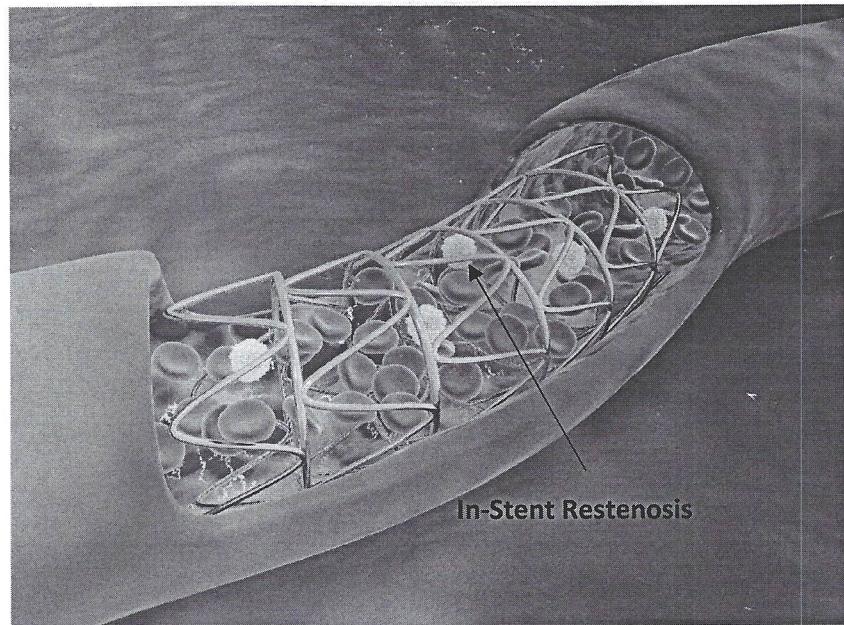
Fig1. Diverse drug-eluting stents are currently available, differing in the type of metal used, stent design, and drug coating [14].

Stent trade name	Metal source	Drug used as coating
Cypher	Stainless steel	Sirolimus (Rapamune)
Endeavor	Cobalt-chromium	Zotarolimus
Taxus	Stainless steel	Paclitaxel (Taxol)
Xience	Cobalt-chromium	Everolimus (Afinitor)
Promus	Platinum-chromium	Everolimus

Table 1. DES Types and corresponding metal and drugs used.

## Restenosis: The Problem

Restenosis, as the name indicates is nothing but the recurrence of stenosis. Restenosis occurs when the treated blood vessel becomes blocked again. Restenosis is usually attributed to an artery or other large blood vessels that had received treatment to clear the blockage and subsequently re-narrowed. It usually occurs within 4 to 6 months after the initial procedures like cardiac surgery, angioplasty, and stenting. If the restenosis occurs following the angioplasty, it is said to be Post-angioplasty restenosis (PARS). If it occurs following the stenting procedure, it is termed as in-stent restenosis (ISR).



Why does in-stent restenosis occur? This can be an obvious question. Let's try to understand the answer to this question. When a stent is placed in a blood vessel, new tissue grows inside the stent, covering the struts of the stent. Initially, this new tissue consists of healthy cells from the lining of the arterial wall. This is a favorable effect because development of normal lining over the stent allows blood to flow smoothly over the stented area without clotting. Later, scar tissue may form underneath the new healthy lining. In about 25% of patients, the growth of scar tissue underneath the lining of the artery may be so thick that it can obstruct the blood flow and produce a blockage. In-stent restenosis is typically seen 3 to 6 months after the procedure [16]. In-stent restenosis can differ from person to person. It is usually at a high risk for the patients with diabetes, as their coagulation and tissue growth factors vary depending on their disease duration. Further important risk factors relate to the properties of the blocked artery and the pattern of scar tissue growth inside the artery; the more extensive the scar tissue growth, the worse the prognosis is [17]. In-stent restenosis may produce symptoms that are very similar to the symptoms that initially brought the patient to the interventional cardiologist, such as chest pain triggered by exertion. Diabetic patients, however, may have fewer symptoms, and unusual symptoms, or even no symptoms at all. Fortunately, a heart attack does not usually occur even if in-stent restenosis develops. The reason and rate of restenosis occurrence in different cardiovascular procedures are shown below.

### Balloon Angioplasty

- Acute/ Chronic Recoil
- 35-60 % Restenosis

### Bare Metal Stents

- Neointimal hyperplasia
- 16-44 % Restenosis

### Drug Eluting Stents

- Stent Thrombosis
- 2-10% Restenosis

## Mechanism of neointimal hyperplasia:

Neointimal hyperplasia refers to proliferation and migration of vascular smooth muscle cells primarily in the tunica intima, resulting in the thickening of arterial walls and decreased arterial lumen space. Neointimal hyperplasia is the major cause of restenosis after percutaneous coronary interventions such as stenting or angioplasty. The term neointima is used because the cells in the hyperplastic regions of the vascular wall have histological characteristics of both intima and normal artery cells. Immediately after stenting, the denuded endothelial surface and disrupted medial tissue of arterial wall due to mechanical trauma triggered an inflammatory process, which led to platelet adhesion, activation, and aggregation, and subsequently fibrin deposition and thrombus formation within the stent [18]. These proliferating smooth muscle cells subsequently migrate into the intima and thrombus in the stent lumen and eventually form a neointimal layer within the stent lumen. Even though cell proliferation ceases at 2 weeks after the initial injury, these smooth muscle cells continue to produce an abundant extracellular matrix, which leads to increased neointimal volume. If this process of neointimal growth is exuberant and significantly encroaches on the vascular lumen, it will lead to ISR [19]. As a deeper vascular wall injury stimulates more neointimal hyperplasia, the stent deployment injury induces more neointimal tissue growth than the BA injury.

## DES: Design and Mechanism

An effective Drug-eluting stent structure generally consists of three parts, (1) Prime Layer: a metallic stent platform, (2) Drug loaded matrix: a polymer coating that binds the drug to the stent and releases the drug. A drug carrier vehicle refers to something that stores a therapeutic agent as well as allows the agent to diffuse into the vascular tissue in a controlled fashion, and (3) Rate limiting barrier: an effective therapeutic agent that reduces the neointimal growth induced by stent implantation. The cross section of the stent structure can be seen in fig 2.

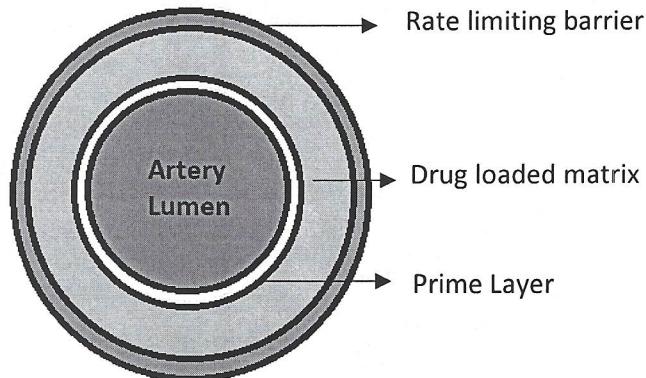


Fig 2. Cross Section of DES structure

The mechanism of drug eluting stents is quite simple and straightforward to understand even though the practical aspect of it is profound and complex. The procedure is exactly similar to that of bare metal stenting. Here, the main difference is the presence of polymer coated with drugs on the metal strut. Once the DES is in the position of the blockage and the narrowed vessel is reopened, the medication or the drugs react with the blood antigen and gradually releases the medications into the artery. This prevents fibrosis that, together with clots, could otherwise block the stented artery or simply say prevents restenosis. The stent is usually placed within the peripheral or coronary artery by an interventional cardiologist or interventional radiologist during an angioplasty procedure.

The effect of different stent designs on the drug distribution pattern has been scrutinized in experimental studies and tested in clinical trials. Recent experimental data suggest that the stent strut configuration directly determines the pattern and degree of drug delivery achieved by DES. The simple proximity of stent struts to vascular tissue does not ensure adequate drug delivery and distribution because most nonuniform distributions have been found in the layers of the artery closest to the stent [20]. In summary, the optimal stent design of drug delivery should have a large stent surface area, a small cell gap, and minimal strut

deformation after deployment while maintaining conformability, radial support, and flexibility to reach the complex coronary lesions [21].

#### Drugs used for coating DES:

Ever since the development of drug eluting stents, the research on the type of drugs used as the substance to treat ISR has been constantly going on. Apparently, the Intervention cardiology has seen two generations of DES and each generation has been categorized based on the substance used as the drugs. We will be further discussing the various drugs used ever since the DES was introduced.

Sirolimus also known as Rapamycin, was the first drug to be used in the first-ever US FDA approved drug eluting Cypher stent in the year 2003. It is an immunosuppressive agent/drug with anti-migratory and anti-proliferative effects on vascular smooth muscle cells that can be used to prevent rejection in organ transplantation [22]. It has also been investigated as an anti-cancer agent owing to its anti-proliferative abilities. The trade brand of DES that used sirolimus as the drug was the CYPHER™ stents.

The Cypher stents comprise of two layers of polymer coated on a balloon expanding BX Velocity™ stent which is made up of stainless steel 316 L, that has been laser cut and electropolished. The conventional bare metal stent is then coated with Parylene C, known for its increased dielectric constant, used conventionally for improving moisture resistance and biocompatibility of biomedical devices [23]. CYPHER has been implanted in more than 3 million patients globally since their approval in 2003. Clinical trials implementing the Cypher indicates that sirolimus is released slowly over four to six weeks with 80% released by the fourth week, and 100% released by the sixth week. Complete elimination of restenosis with these stents was a result of the reduction in hyperplasia, and thus, no additional treatment for these patients was needed [24]. However, sirolimus had few limitations too. The incidence of late stent thrombosis has marked their long-term success due to hypersensitivity and inflammatory reactions. In few cases, there have been reports confirming the occurrence of acute/subacute stent thrombosis within 24 hours or 30 days as well [24]. Local hypersensitivity to the sirolimus eluting stents characterized by eosinophils, lymphocytes, and giant cells

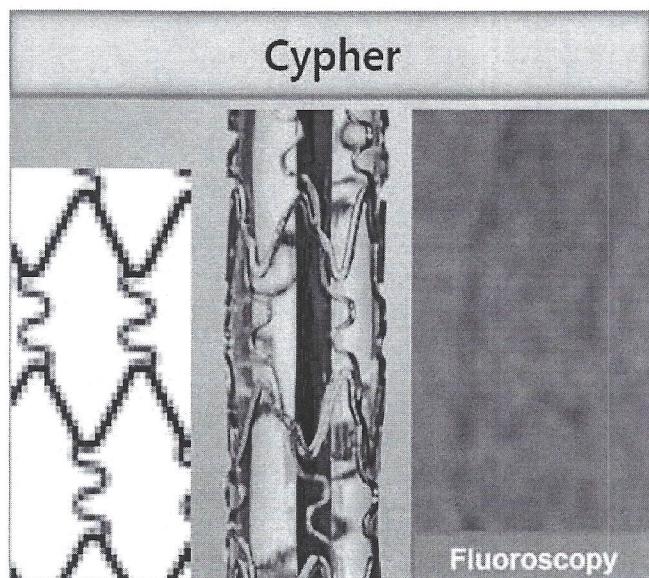
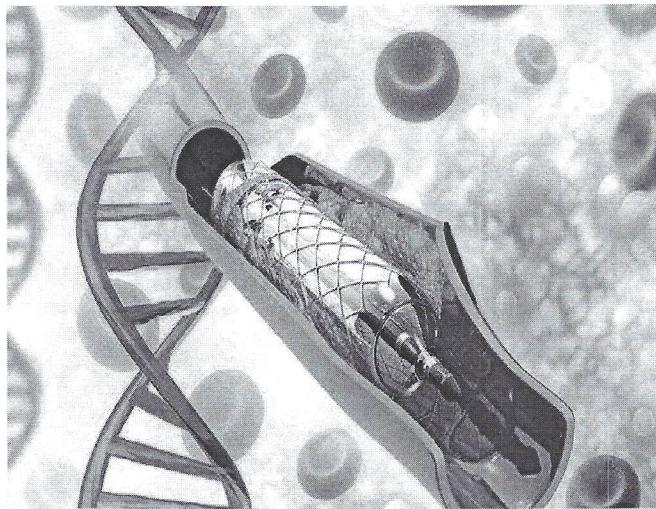


Fig 3. Showing the type of metal used, stem design and fluoroscopy image of CYPHER.

throughout the stented segment was found to greatly contribute to the late-stent thrombosis. Thus, these limitations led to the rise of another type of drugs known as paclitaxel.

The National Cancer Institute's plant extract screening program for an antitumor activity led to the discovery of paclitaxel, which was approved by the FDA for its antineoplastic use for ovarian cancer treatment in 1992. A flurry of clinical trials soon after the FDA approval of sirolimus-eluting stents in 2003 fronted the way for the FDA approval of paclitaxel-eluting TAXUS stents in 2004 [23-25]. The Taxus® stent developed by Boston Scientific comprises of a triblock copolymer that includes a hydrophobic moiety in the form of isobutylene, which can better associate with the hydrophobic drug paclitaxel and enhance loading and release kinetics of the same. However, the incidence of in-stent thrombosis with long term usage of the Taxus stents has been a major cause of concern from the standpoint of their utility as anti-restenosis devices.

The limitations of sirolimus-eluting and paclitaxel-eluting stents led to the rise of second generation drug eluting stents. Endeavor® (Medtronic, Inc., Minneapolis, MN) was approved by the FDA in February 2008. The Endeavor® stent uses Abbott Vascular's zotarolimus drug and a cobalt alloy stent coated with a biocompatible phosphorylcholine coating on Medtronic Vascular's cobalt-chromium based Driver™ metallic stent platform [25-26]. Zotarolimus is the first ever drug synthesized exclusively for the treatment of in-stent restenosis. Zotarolimus is produced by the tetrazole ring substitution of the hydroxyl group at the C<sub>42</sub> position. The presence of a tetrazole ring instead of a hydroxyl group makes zotarolimus extremely lipophilic. This hydrophobicity restricts the solubilization of zotarolimus in the luminal blood flow; leading to an immense decline in the systemic exposure risk and the negligible concentrations of the anti-proliferative agent also tends to be conducive to stent re-endothelialization [27].

Another well-known drug used to prevent ISR in the second-generation DES is everolimus. Unlike the extremely lipophilic zotarolimus, everolimus is a relatively polar immunosuppressant macrolide with a 2-hydroxyethyl chain at the C<sub>40</sub> position of sirolimus. The everolimus eluting stent Xience V™ (Abbott Laboratories) is another second-generation drug eluting stent, which got approved by the FDA in July 2008. In addition to a change in inhibitor and different polymeric platform, these stents also have some changes in their stent design that may add to their therapeutic utility and minimize late/very late endothelial response generator [28]. The major limitations of sirolimus-eluting stents were mainly due to platelet aggregation resulting from a lack of endothelial surface coverage of the stent, mainly due to adequate blood plasma concentration of sirolimus which resulted in a thrombogenic response to the stents. The possibility of such an adverse eventuality is significantly minimized with everolimus eluting stents.

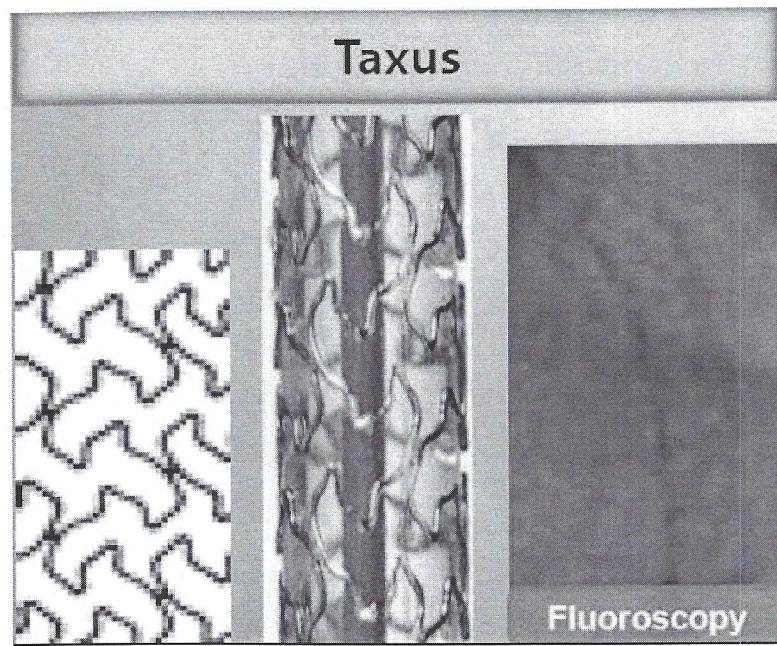


Fig 4. Showing the type of metal used, stem design and fluoroscopy image of TAXUS.

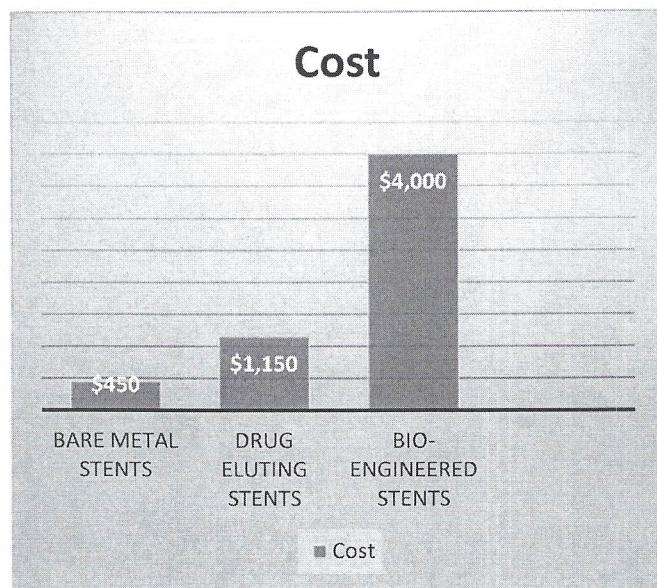
## **DES VS Others: Cost Differences**

According to Healthcare Finance News, the delivery of coronary artery stents is a procedure that affects over 1 million patients each year in the United States. With an aging population, the declining cost of stents and reimbursement tracking with the consumer price index (2-4 percent margins), the market for stenting is expected to grow continuously. Two main types of stents are currently offered in the U.S. market: bare-metal stent (BMS) and drug-eluting stent (DES). DES, which were developed to combat the restenosis issues of the BMS, account for most of stenting procedures done today.

A few years back, the price of stents was too high. Lately, the healthcare domain has seen the downward pricing of stents due to competitions between various coronary stent manufacturing companies. The original BMSs were priced at \$1,595, and DES prices were set at a sky-high price of over \$3,000. With the stiff competition spread over main vendors, prices have seen a sharp drop, to as low as \$450 for BMSs and \$1,150 in DESs [28]. The cost estimation of three different generations of stent technology can be seen in fig 5. Even though the cost of DES is slightly more than that of bare metal stents, the rate of restenosis is quite low which can be a real advantage and eliminate the drawback of being costlier than the previous treatment methods. The ever-increasing competition between the leading stent manufacturing companies might reduce the cost furthermore.

## **DES RISKS**

Everything in this world has pros as well as cons and so does the drug-eluting stents too. The medications released from drug-eluting stents inhibit cell proliferation and activate signal transduction pathways. Consequently, although these stents are designed to prevent the proliferation and migration of vascular smooth muscle cells, they can also disrupt reendothelialization. This slows healing of the artery, as well as increasing the expression of tissue factors, which can lead to a prothrombogenic environment and the development of a clot inside the stent. This is referred to as stent thrombosis, a complication that is rarely seen with bare-metal stents. These clots can occur months or even years after the drug-eluting stent is implanted and can increase the risk of heart attack and death. Patients are therefore prescribed anticoagulants to reduce the risk of clotting within the drug-eluting stent [29]. However, researchers are not sure how long these medications need to be taken for, as it is not known how long the vessel takes to completely heal after the insertion of a stent. The long-term use of anticoagulants can also be an unappealing option for people with bleeding problems or those who require further surgery within a year of stent placement. The use of drug-eluting stents has been successful in many people with heart problems, reducing the need for more invasive surgeries such as coronary artery bypass. Furthermore, the reduced rates of restenosis in patients who have a drug-eluting stent has significantly reduced the need for repeat angioplasty, which is associated with risks such as stroke and heart attack [30]. Although DES was proved to be a safe and effective method in the treatment of coronary artery stenosis by both randomized clinical trials and real-world practice, its expanded indications in complex and high-risk lesions for restenosis such

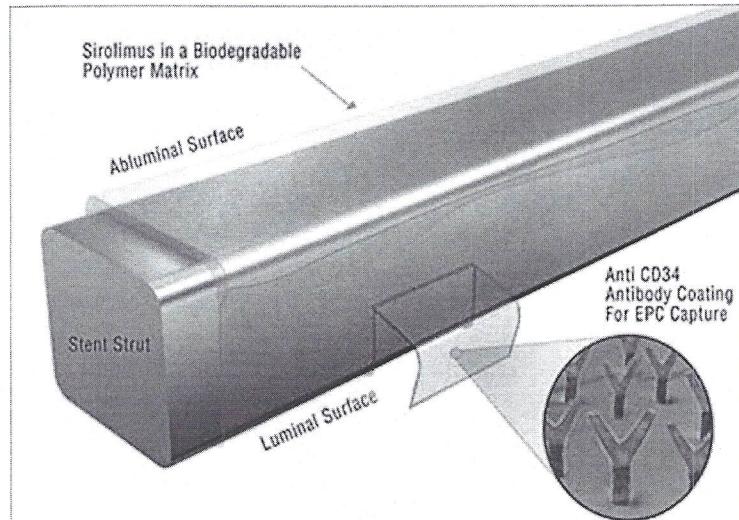


as occluded lesions, left main lesions, bifurcation lesions, ostial lesions, small and long lesions, saphenous vein graft lesion, ISR, and diabetes mellitus are still under evaluation with ongoing trials. The results of clinical trials for some expanded indications are now available.

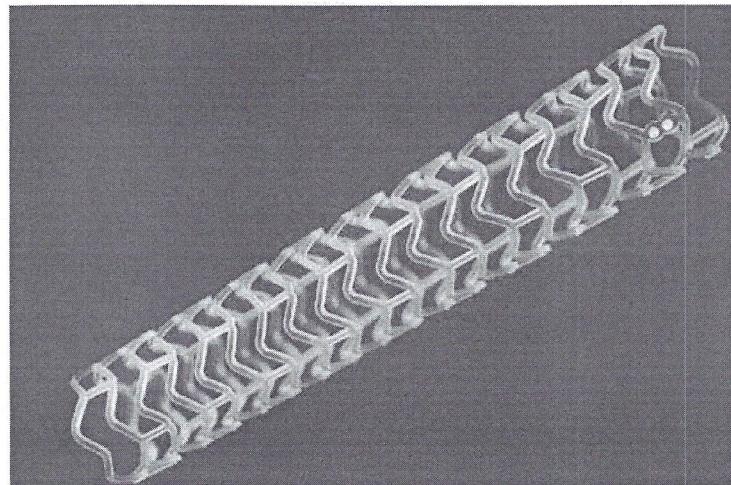
## Future Trends

The future of Interventional cardiology shall see tremendous improvement in the stent technology. Many third generation and fourth generation stents are undergoing clinical trials and awaiting FDA approvals. Few among them are discussed below.

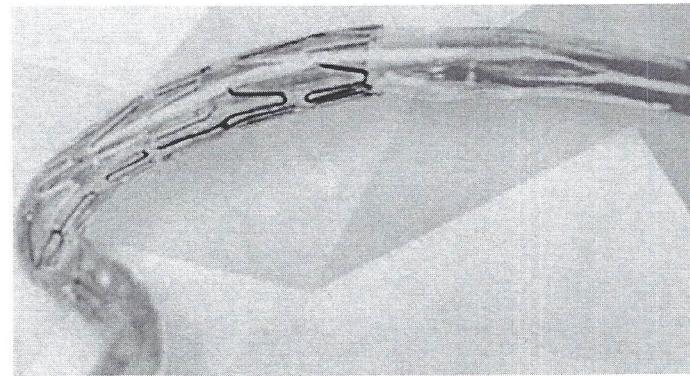
Dual Therapy Stent (DTS) is the latest type of coronary stent. It is kind of stent therapy designed to not only reduce the likelihood of the re-narrowing of the artery or of having to undergo a repeat procedure, but also help the healing process of the artery. It combines the benefit of DES and bio-engineered stents and is the only stent to contain a drug with active healing technology. The DTS has coating both inside and outside, which reduces the possibility of blood clots, inflammation and helps the healing process of the artery [31]. The stent surface facing the artery wall contains a drug that is released to help stop the artery blocking again without the worry of swelling or an inflammatory response. The drug is delivered from a bio-resorbable polymer that will degrade over time. The side of the stent which faces blood flow is coated with antibodies, which promote natural healing and helps the healthy artery function properly [32].



Bioresorbable Vascular Scaffold: The Bio-Vascular Scaffold (BVS) is a drug eluting stent on a dissolvable type of scaffold platform which can be absorbed by the body over time. Like some of the currently available Drug Eluting Stents (DES), BVS is coated with a drug released from a polymer that disappears over time to reduce the occurrence of the artery re-narrowing. The scaffold itself is absorbed over time. Unlike the dual therapy stents, there is no active element to promote artery healing.



**Bio-engineered Stent:** Bio-engineered Stent is also known as an antibody-coated stent. This type of stent differs from DES as it does not contain a polymer and does not use a drug. As a result, it helps to speed up the cell lining of the artery or endothelialization. Hence, promoting natural healing. The antibody on the stent's surface attracts circulating Endothelial Progenitor Cells (EPCs) which come from human bone marrow and help speed up the formation of healthy endothelium. This provides quick protective coverage over the stent's surface, helping to reduce the risk of early and late thrombosis [33].



### Clinical Trials

One of the earliest clinical trials on the DES was on the first-generation stent types which used sirolimus as drug eluting substance. This clinical trial was named as First In Man (FIM) study. The study consisted of 45 patients with angina pectoris. From the observation of this clinical study, it was concluded that there were no major cardiac events like myocardial infarction, coronary bypass grafting, or target revascularization (TLR) for the time up to 2 years of clinical follow up. The only after effects seen in few patients under study was minimal neointimal hyperplasia within the stent. This was re-diagnosed during angiographic and intravascular ultrasound (IVUS) follow-up at 1 year; and 10% TVR rate for the entire cohort at 2 years [34].

The next set of clinical trials to be discussed is about the usage of Paclitaxel as a drug eluting substance. Unlike SES, paclitaxel and its derivatives have been studied in different coatings and stent designs. In this study three main coatings of paclitaxel were considered: (1) 7-hexanoyltaxol which used polyacrylate sleeves as a release mechanism tested in the SCORE (Study to compare restenosis rate between QuaSt and QuaDS-QP2) trial; (2) Paclitaxel-eluting stent (PES), which used non-polymer coating as platform tested in 3 other trials; and (3) PES which used polymer coating as a platform tested in TAXUS I–VI trials [35]. Except for the polymer-coated-PES, the other two types of coating have not been very suitable or useful [35-36]. The initial feasibility study of polymer-based PES, TAXUS I, was performed in Europe where the feasibility of using a PES to treat short lesions was demonstrated.

TAXUS II was the first randomized trial using both slow-release (SR) and moderate release (MR) PESs. Interestingly, it had a binary restenosis rate of 5.5% in SR and 8.6% in MR, respectively [37]. TAXUS III was a feasibility trial of SR-PES in ISR with the result of feasible and safe use in the treatment of ISR in 28 patients with a major adverse cardiac event (MACE) rate of 29% [38]. TAXUS IV, a major pivotal American trial of PES compared with BMS, showed significant reduction in the TLR rate (4.4% vs 15.1%), TVR rate (7.1% vs 17.1%), and composite MACE rate (10.8% vs 20.0%) [39]. TAXUS VI was a randomized trial using MR-PES in complex lesions such as very long lesions or lesions in small vessels. The results showed in-stent binary restenosis rate of 12.4% vs 35.7%, TLR rate of 6.8% vs 18.9% and TVR rate of 9.1% vs 19.4% when comparing PES with BMS arm at 9 months [35-40].

Stents coated with rapamycin analogues and everolimus were also studied in clinical trials. The next set of clinical trials performed was the ENDEAVOR I trial. It was a randomized controlled trial to evaluate the safety and efficacy of the Medtronic AVE ABT-578-eluting driver™ coronary stent in de novo native coronary artery lesions, ABT-578 (Abbott Laboratories, Abbott Park, IL, USA) coated cobalt-alloy stent

(Driver stent, Medtronic Inc, Minneapolis, MN, USA) was used to treat 100 patients with de novo lesions. In this study, the result showed 0.33 mm of angiographic in-stent late lumen loss at 4 months and 0.58 mm at one-year follow-up. The target-vessel failure rate was comparable to the results of SIRIUS or TAXUS IV [41]. ENDEAVOR II and III are large pivotal trials for ABT-578 and the results are pending. FUTURE (First used to underscore reduction in restenosis with everolimus) I and II trials were designed to demonstrate the safety and feasibility of the everolimus-eluting-stent (Novartis Pharma AG, Basel, Switzerland) in a small population with focal de novo coronary artery lesions with an in-stent late lumen loss of 0.12 mm, a low TLR rate (4.3%) and a very low MACE rate (6.4%) at 6-month follow-up [42]. A large clinical trial for everolimus eluting stent is ongoing. The bigger stent manufacturing companies like Abbott laboratories, Medtronic, and Boston Scientific are always in the hunt to advance and upgrade their existing DES models and hence, in the future, better technologies in the field of interventional cardiology can be expected.

### **Conclusion:**

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Development of Drug-Eluting Stent is a considerable advance in interventional cardiology, rivaling the impact of angioplasty and stenting. From various studies, it can be concluded that DES dramatically reduces the ISR rate in all subgroups of patients in both randomized clinical trials and real-world practice. However, cost constraints and lack of re-stenting reimbursement have limited their utilization in daily practice in many developing countries. Perhaps, initial analyses of the sirolimus-eluting stent have shown a highly favorable cost-effectiveness profile in reducing repeat revascularization and combined major cardiac events. The future of interventional cardiology might see drastic changes in the stenting techniques or who knows one day it might get completely eliminated with the introduction of Nano-vacuum extraction of cholesterol deposition in the artery and thereby clearing the blockage. Meanwhile, continuing improvement in drug-delivery stent technologies and gradual reduction in cost would make DES an effective mainstay of therapy for coronary artery disease.

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