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CORONARY ARTERY STENT: HISTORY, TYPES, MANUFACTURING PROCESS

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ABSTRACT

Coronary artery disease is the greatest cause of death worldwide. Atherosclerosis is caused by the deposition of plaque. Current pharmacological anti-atherosclerotic modalities that are still unsuccessful in controlling the disease and improvements in clinical interventions are urgently needed. Blocked atherosclerotic arteries are treated with an expandable metal stent in hospitals. Various types of stents are available on the market to treat clogged cardiac arteries and reduce the risk of heart attack. Herein, the current stent technology and their manufacturing processes are reviewed.

INTRODUCTION

Coronary artery disease (CAD) is the narrowing of arteries in the heart. This narrowing also called as stenosis. Stenosis is defined as, narrowing or contraction of a blood vessel or valve which reduces blood flow. Stenosis is caused by deposition of fat, waxy or calcium in the artery wall called plaque. This process called as atherosclerosis. About 31% of death in the world caused by Coronary Artery Disease. There are various options are available for treatment coronary artery disease (CAD). Coronary Stent is one of the this treatment option.

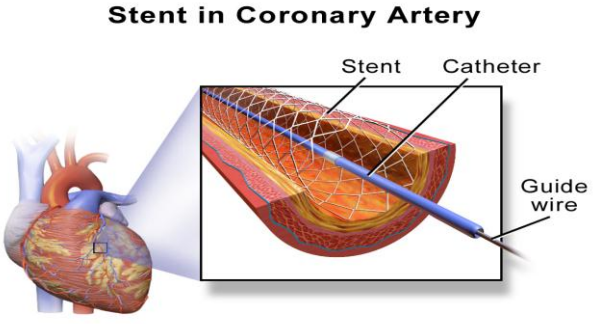
History of Stents

Coronary angioplasty,first established in 1964 by Dotter and Judkins, was first performed in 1977 by Andreas Gruntzig.[1] In 1979 Geoffrey Hartzler First balloon angioplasty performed to treat AMI. Coronary stents were developed in the mid-1980 and since then, design and composition have largely been clarified. The first coronary stent implanted in a human coronary artery i.e. WALLSTENT (Schneider AG), a self expanding, stainless steel wire-mesh structure, by Sigwart et al. in 1986.[2] Schatz and co-workers developed the Palmez-Schatz (Johnsons & Johnsons) stent in 1987, this is the first FDA approved stent in USA.[3] Many other different stents were developed in 1990 which include: Flexstent (Cook), Wiktor (Medtronic), Micro (Applied Vascular Engineering), Cordis (Cordis) and Multilink (Advanced Cardiovascular System).[4] In 1991, Cannon and Roubin played First Coronary stenting for the treatment of AMI.

In 1993 two pioneering attempts, the Belgian Netherlands Stent Arterial Revascularization Therapies Study (BENESTENT) and North America The stent restenosis study (STRESS) showed that bare metal stents are superior (BMS) over POBA, which establishes the implantation of coronary stents as an accepted standard care for PCI.[5]

What is stent?

Stents are small expandable tubes used for treatment narrowed or constructed arteries in the body. Stents are used to treat Coronary Artery Disease (CAD) through the opening of blockage or clog arteries which help to reduce risk of angina and heart attack. This stent is referred as Coronary stent. Stents are mostly made up of metal mesh. Coronary stents are introduced in narrowed coronary arteries to prevent the artery from becoming blocked again (restenosis).



Types of Stents

Dual Therapy Stents (DTS)
Bioresorbable Vascular Scaffold (BVS)
Bio-engineered Stent
Drug Eluting Stent (DES)
Bare Metal Stent (BMS)

1.Dual Therapy Stent: A dual therapy stent is used as coronary artery stent that is the combination technology of a bioengineered stent and a drug eluting stent to both acce-lerate healing of the vessel and to block cell proliferation.[6] The Combo Dual Therapy Stent is the first stent to combine a luminal anti-CD34 antibody with antiproliferative abluminal sirolimus elution. It is composed of a abluminal coating of bioabsorbable polymer matrix formulated with sirolimus (5 mcg/mm of stent length) for sustained release and a luminal anti-CD34 antibody cell capture coating. The increasing interest in the because combo stent of its safety, feasibility and efficacy.[7]

2.Bioresorbable Vascular Scaffold (BVS): BVS is used as antirestenotic drugs identical to the second generation DES, but the entire scaffold resorbs over several years. The bioresorbable vascular scaffold is formed either by a polymer or a biodegradable metal rather than a durable metal. BVS aims to provide adequate radial support the release of antiproliferative drugs is prevented for a period of time long enough to avoid recoil Restenosis. BVS consists of a bioabsorbable poly (L-lactide) (PLLA) backbone and a bioabsorbable PDLLA coating that contains everolimus. The semi-crystalline PLLA replaces Metal alloys with load-bearing material. According to Abbott, the device is referred to as a scaffold rather than a stent because the term stent indicates permanence while a BVS provides structure temporarily before finally being completely absorbed. It is believed that the potential for late stent thrombosis is reduced for a device that disappears, and it was suggested that unlocking the artery would allow the natural to be restored Vasoreactivity and late lumen enlargement.[8] Some different bioresorbable scaffolds at different stages of development, including Igaki-Tamai (Igaki)Absorbw BVS (Abbott Vascular), REVAw (Reva), ReZolvew (Reva), Ideal BioStentw (Xenogenics), etc.[9]

3.Bio-engineered Stent: A Bio-engineered stent is a new form of alternative used in heart stent surgery. Bio-engineered stents first received approvals in Europe and have been experiencing wide-spread adoption ever since. They are constructed of cobalt and chromium fabric, which is thinner and more flexible and chromium with the Endothelial Progenitor Cell (EPC) technology, which enables the healing of the infarct area and develop its cell walls over time. These biotechnologically manufactured stents have a Dual helix stent design, making them optimal for a longer duration. EPCs also protect against thrombosis and modular restenosis.

4.Drug Eluting Stent: Drug Eluting Stent is used to treat Coronary Artery Disease (CAD) by implanting drug eluting stent in artery. In 1999, Sousa established the first DES in Brazil, signaling the third revolutionary paradigm shift in the history of interventional cardiology. A drug eluting stent is coated with slowly release medication. DES is a coronary stent placed into narrowed, diseased peripheral or coronary arteries that slowly releases a drug to block cell proliferation. Analysis of randomized DES trials revealed an increase in very late (>1 year) stent thrombosis in both paclitaxel and sirolimus eluting stents, a risk which appeared to persist at a rate of 0.35–0.6% annually. DES thrombosis is associated with a mortality of 20–40% and myocardial infarction of 50–70%.[10] The rate of stent strut endothelialization, occurring significantly faster in BMS, this is the main difference between the BMS and DES.[11]

First generation DES

First generation drug eluting stents Sirolimus and paclitaxel were the two antiproliferative agents originally used in first generation DESs (or CYPHER) [Cordis, Milpitas, CA] and TAXUS [Boston Scientific, Marlborough, Massachusetts]). Both were made of stainless steel and had a strut Thickness greater than 130 mm and have been tested in numerous randomized controlled trials shows a significant reduction in ISR, late lumen loss and target rate Lesion / vascular revascularization compared to BMS.

Second generation DES

In second generation DES, the platform was converted to metal Alloys (ie cobalt chromium or platinum chromium) that allowed a reduction in the strut thickness and more flexibility. Polymers have been made from new, more biocompatible materials molecules such as Zotarolimus, Everolimus and Novolimus (the Limus family drug), with faster and later drug elution previous endothelial coverage. The safety and effectiveness of DES was the second generation evaluated in numerous RCTs that show significant reductions in rates of MI, target lesion revascularization and ST versus First generation DES. Given these advances, the second Generation DESs are the most widely used DESs worldwide and they are accepted as percutaneous treatment of choice for CAD, completely replaces BMS and DES of the first generation.

Polymer free DES

The polymer shell is involved in pathogenesis long-term Stent failure by triggering a possible chronic inflammation Stimulus responsible for delayed endothelial coverage and ST. Hence a new strategy to eliminate polymer-mediated complications was the development of polymer-free DES that can theoretically avoid these long-term negative effects, decrease the ST rate and allow a shorter DAPT duration. However, since the polymer does not only act as an active ingredient carrier, it does also modulates the controlled release of the drug over time. The development of polymer-free DES required a new technolog to maintain an adequate level of antiproliferative drug over time without the polymer vehicle.

Biodegradable polymer stent

Drug-eluting stents that are coated with biodegradable polymers (e.g. B. Poly-DL-lactide-co-glycolide or PLLA) can take advantage of conventional DES in the

early phase and later stages behave like a BMS. The bioresorbable polymer is degraded simultaneously with controlled release of the antiproliferative drug in the early phase after implantation. After complete elution of the drug and the biodegradation of the polymer, only the metal platform remains in the coronary artery. Several organic currently resorbable polymers are used, which differ biocompatibility, degradation time and their different effects on endothelial function, growth of smooth muscle cells and Thrombogenicity.

Table: Types of Drug Eluting Stents.

	Manufactured by	Series	FDA APPROVAL	Platforms	Diameters (mm)	Length (mm)
Sirilimus stents:	Johnson & Johnson and cordis	Cypher	04/23/03	316L stainless steel Bx velocity stent	2.25, 2.50, 2.75, 3.00, 3.50	8, 13, 18, 23, 28, 33
Paclitaxel stents:	Boston Scientific	Taxus	03/04/04	316 stainless steel Express 2 stent	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	8, 12, 16, 20, 24, 28, 32, 38
Everolimus stents:	Guidant and Abbott	Xience V	07/02/08	L605 Cobalt chromium alloy ML Vision stent	2.25, 2.50, 2.75, 3.00, 3.50, 4.00	8, 12, 15, 18, 23, 28
Zotarolimus stent	Medtronic	Endeavor	02/01/08	Cobalt chrom driver stent	2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 4.50	8, 12, 18, 24, 30

Table: Recent advances in drug-eluting stent design.[12]

Table 1. Recent advances in drug-eluting stent design.

Stent name	Design feature	Drug eluted	Drug elution time	Latest clinical trial result
Polymer-free DES				
VESTA-Sync™	Hydroxyapatite coating	Sirolimus	4 weeks	Late loss superior to BMS (8 month) [35]
Amazonia PAX	Microspray crystallization	Paclitaxel	45 days	Similar late loss to Taxus at 4 months [37]
Biofreedom™	Microabrasion texturing	Biolimus	28 days	Noninferior to Taxus at 12 months [39]
Yukon®	Microporous	Sirolimus	21 days	
DUAL-DES	Yukon analog	Sirolimus/Probucol	56 days	Superior to Cypher® at 2 years [46]
Biodegradable polymer DES				
Biomatrix	PLA coating	Biolimus	90 days	Lower MACE than Cypher at 3 years [54]
Nobori®	Parylene layering	Biolimus	6–9 months	Safety shown in 1-year registry [57]
Supralimus™	PLLA/PLGA	Siroliumus	48 days	7% MACE at 30 months, 0.6% ST [58]
Infinnium™	Supralimus analog	Paclitaxel	49 days	Reduced TLR vs BMS at 9 months [60]
Yukon® Choice	Proprietary coating	Sirolimus	4 weeks	Similar to Cypher, Xience at 3 years [62]
JACTAX	PLLA microdots	Paclitaxel	90 days	Noninferior to Taxus at 6 months [52]
Costar	Strut reservoirs	Paclitaxel	30 days	Inferior to Taxus [49]
Nevo	Costar analog	Sirolimus	90 days	Trend to superior over Taxus 1 year [50]
Synergy™	PLGA	Everolimus	90–120 days	Noninferior to Promus Element™ Plus [65]
Orsiro	Silicon carbide/PLLA	Sirolimus	100 days	Noninferior to Xience Prime [68]

BMS: Bare-metal stent; DES: Drug-eluting stent; PLA: Polylactide; PLGA: Poly(lactic-co-glycolic acid); PLLA: Poly-L-lactic acid; TLR: Target lesion revascularization.

Bare Metal Stent (BMS): Bare Metal Stent are usually stainless steel and it does not having any special coating. Stainless steel BMS were the first devices used for coronary stenting. They act as scaffolding to open blood vessels after they are widened with angioplasty recently bare metal stent are made up of stainless steel, cobalt chromium, or platinum chromium. Coroflexw (B-Braun), Driverw (Medtronic), Visionw (Abbott Vascular) this BMS are made up of cobalt –chromium. The most recent development in the stent platform is the use of the Element Platform, which is made up of a platinum–

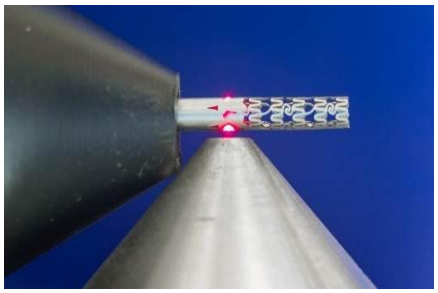
chromium alloy, as in Omegaw stent (Boston Scientific).[13]

Manufacturing processes for Stent

There are different types of manufacturing processes are available for Stent.

1. Laser Cutting
2. Photo Chemical Etching
3. Micro-EDM
4. Electroforming

1. Laser Cutting: The first Ruby laser is demonstrated in 1960 by Theodore Maiman.[14] The research in laser has progressed with the development of different types of lasers for different applications such laser cutting, welding, drilling and surface engineering.



Process: Laser cutting is the process in which high intensity laser beam is used to rapidly heat material, consistently melting or vaporising the material. The generated molten material and vapour is blown out from the cut kerf by an assist gas jet.[15] The use of oxygen as an assist gas jet potentially increases the efficiency of the process due to the exothermic reaction with certain material at high temperature to add additional exothermic energy. The laser beam is focussed by a focussing lens down to a smallest spot. Small spot size is preferred during the cutting process for a specific material removal and high accuracy. Coaxial gas is delivered through a nozzle in the same direction with the laser beam. The introduction of assist gas is to enhance the ejection of melted or vaporised materials out of the kerf. Figure 1 shows the basic outline of the laser cutting.

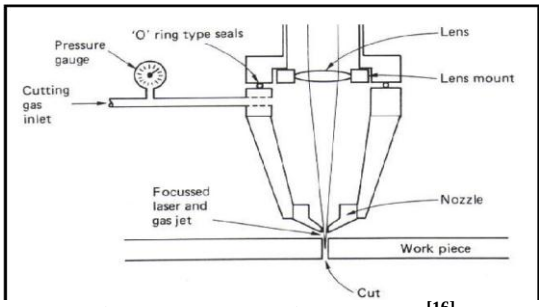


Figure: Laser cutting process.[16]

2. Micro-EDM: In micro-EDM, the material removal takes place by electro-erosion due to electric discharge generated between closely spaced electrodes in the presence of a dielectric medium. The shape of the machined feature is the mirror image of electrode.[17]

3. Electroforming: In this process, electroplating is performed on a mandrel in a given pattern. The mandrel is etched away from the electroformed stent, leaving a free standing structure, a fully functional stent when the desired thickness has been reached.[18,19]

4. Photo Chemical Etching: Photo chemical etching process is based on the photolithography process. In this process, the desired mask pattern is first projected on the plain sheet coated with photoresist, with after exposure can be developed and etched for the desired pattern.[20]

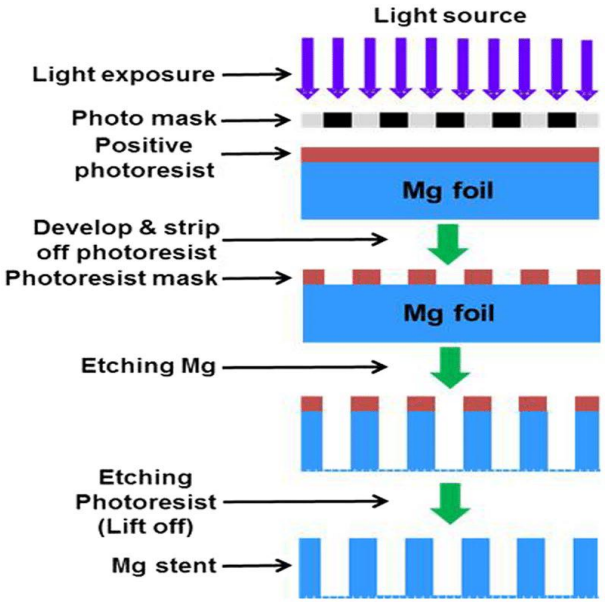


Figure: Manufacturering process of Photo Chemical Etching.

CONCLUSION

Coronary artery stenting is the treatment of choice for patients who need coronary angioplasty. There are various ongoing studies evaluating newer stents platforms, anti-proliferation agents, novel polymers, polymer-free stents and bioresorbable stents.

The search for the ideal stent continues, but maybe not be a single stent suitable for all patients and lesions. There have been significant development in the design of stents. In future interventional cardiologists will have a variety of stents available can allow them to practice evidence-based personalized medicine wherever they choose of the stent is based on genetic determinants, risk profile (for restenosis, thrombosis and bleeding) and lesion characteristics of individual patients.

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