Design and Manufacturing of Micro structured Stents

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Abstract

Coronary angioplasty, also called percutaneous coronary intervention, is a procedure used to open clogged heart arteries. It is often combined with the placement of a small wire mesh tube called a stent. Most stents are coated with medication to help keep your artery open (drug-eluting stents) These stents use Polylactic Acid (PLA) as a carrier for drugs. The stent is coated with a PLA as a drug carrier. Use of PLA causes the recoil of the strength and also increases size, therefore decreasing maneuverability. This research aim at reviewing current state of technology and gaps in stents. The research also aims at developing micro-structured surfaces as a means to carry drugs through the pores. Manufacturing techniques, materials and design of the possible stent is proposed below.

Keywords: Bare Metal Stents (BMS), Drug-eluting stent (DES).

Background

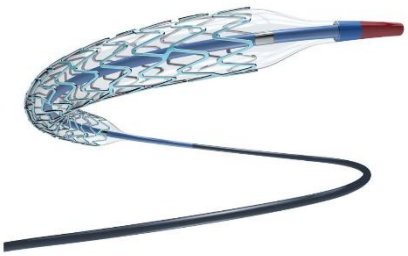

Figure 1 Stent by Boston Scientific

According to a report by Harvard Medical School, each year, about 600,000 people in the United States undergo an angioplasty to widen a narrowed coronary artery. Coronary artery disease is caused by plague buildup in the wall of the arteries that supply blood to the heart, called as the coronary arteries. Plague buildup can cause the inside of the arteries to narrow and clog overtime. This process is called artherosclerosis. Atherosclerosis is the most common form of arteriosclerosis, which is a general term for several disorders that cause thickening and loss of elasticity in the arterial wall. Atherosclerosis can affect all large and medium-sized arteries, including the coronary, carotid and cerebral arteres; the aorta; its branches; and major arteries of the extremities. It is the leading cause of morbidity and mortalilty in the US and in most developed countries. (1)

Epidemiology

Coronary heart disease (CHD) is the primary cause of death in the Western world. It kills over 370,000 people annually. On an average, about 735,000 Americans have a heart attack every year. Out of these, 525,000 have an initial attack, and 210,000 have a recurrent attack. Reports suggest that plaque rupture is the reason for 75% of acute myocardial infarctions. Highest incidence of plaque rupture was observed in men over 45 years; whereas, in women, the

incidence increases beyond age 50 years. This higher prevalence of atherosclerosis in men compared to women is attributed to the protective function of female sex hormones but is lost after menopause. (2)

Stroke from any cause represents the fifth leading cause of death and the major cause of serious long-term disability in adults in the United States. Reports suggest that nearly 795,000 people suffer from stroke every year in the US resulting in about 140,323 deaths. The major form of stroke, ischemic stroke is due to Atherosclerotic Cardiovascular Disease (ASCVD).

Many epidemiologic studies in North America and Europe have recognized numerous risk factors for the development and progression of atherosclerosis. They may promote atherosclerosis through their effects on low-density lipoprotein (LDL) particles and inflammation. (2)

Pathophysiology

Atherosclerosis mainly develops through the continuous process of arterial wall damage which is caused by lipid retention. The lipid is trapped in the inner wall of the arteries, known as intima, by a matrix of proteins such as proteoglycans which results in its modification which, in turn, exacerbates chronic inflammation at vulnerable sites in the arteries. This plays an important role at all phases of the atherogenic progression. (3)

Nascent fatty streaks in the inner wall of the arterial intima evolve into fibrous plagues and emerges into complex atherosclerotic damage that are prone to rupture. In addition, inward expansion of the atheroma can result in closure if coronary vessels. This process is a series of histoligical developments or a series of different classes of coronary damage that may be visible to the unaided eye.

Staging

There are major histologic changes in the development of atherosclerosis approximately in their order of occurrence. (3)

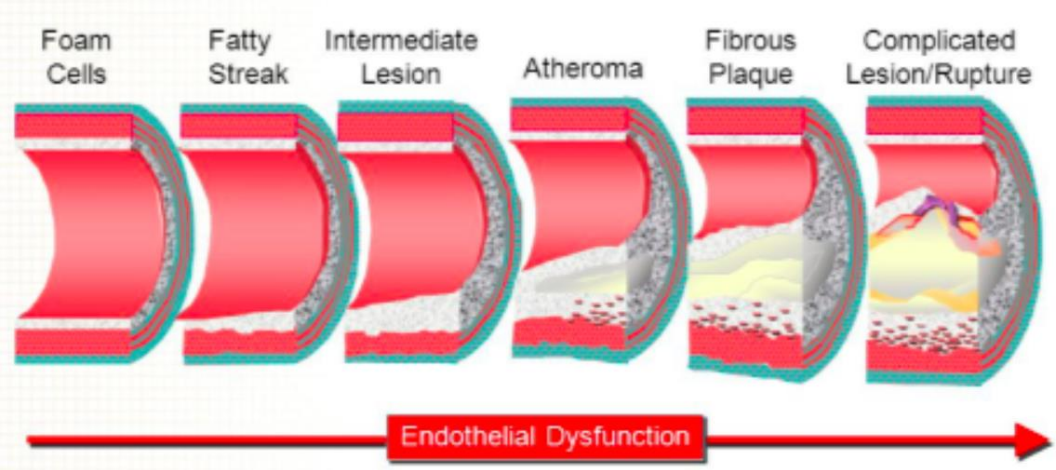

Figure 2 Development process of atherosclerosis

The Early Fatty Streak Phase

The location of the lesion-prone region are relatively constant and predictable and can be seen with an unaided eye. Early fatty lesions begins in childhood. The adaptive thickening is present from birth and in areas of high oscillatory shear index which can be characterized by retention of modified lipoproteins in the intima. This is aggravated by several conditions, which will be described later in the paper, which causes endothelial dysfunction. shift of the properties of the endothelium toward a phenotype characterized by impaired vasodilation and a proinflammatory and prothrombic status. After that there is an increase in the adhesion of monocytes and lymphocytes. Endothelial dysfunction leads to increased junctional permeability manifested by transendothelial migration of immune cells and atherogenic lipoproteins into the arterial intima. Further, the monocytes in intima mature into resident macrophages, which imbibe modified lipids and become foam cells which is a characteristic feature of the early fatty streak lesion. (3)

Early Fibro Atheroma Phase

Migration of smooth muscle cells from the media into the intima following foam cell formation. These cells are crucial in the generation of the collagen-enriched fibrous plaque which is located under the endothelium and is considered the protector of the vessel wall from plaque rupture. Lymphocytes, CAMs, P-selectin, cytokines and chemokines are mediators of inflammation which play a role in a atherosclerosis. (3)

Advancing Atheroma: Thin-Cap Fibroatheroma and Its Rupture

Degeneration of the walls of the arteries caused by accumulated fatty deposits and scar tissue, known as atheroma, appears at about age 55 to 65 years. The thin-cap atheroma is surrounded by a necrotic core heavily infested by cholesterol-enriched macrophages, cholesterol crystals and T lymphocytes and susceptible to rupture. The uncontrolled enzyme activity weakens the fibrous cap which exposes the intima and a thrombus via tissue-factor activation and platelet aggregation that extends into the arterial lumen. This lesion is known as a vulnerable plague (3).

Plaque Rupture

Plague rupture is the region of fibrous cap rupture in which the overlying thrombus interacts with the original necrotic core, followed by the left and right circumflex coronary arteries. (3)

Growth and Development of the Necrotic Core

This is a pathogenic process that contributes to plague vulnerability. The repeat intraplague hemorrhage leads to necrotic core expansion. This leads to a free flow of red blood cells are enriched with lipids and a rich source of free cholesterol. This leads to macrophage cell death in plague, which causes an accumulation of dead macrophages. This is an important pathogenic process contributing to plaque vulnerability. Studies have shown that repeat intraplaque hemorrhage is a contributing feature to necrotic core expansion as red blood cells are enriched with lipids and a rich source of free cholesterol, which is an important constituent of ruptured plaques. Micro-vessel density is increased in advanced plaques by a dysregulated

neovascularization. Thus, intraplaque hemorrhage together with the death of macrophages coupled with defective phagocytic clearance is one of the primary reasons behind necrotic core expansion in advance stage (3).

Plaque Erosion

Plague erosion is typically characterized by no endothelium at the site of erosion, minimal inflammation, and the exposed intima mainly composed of smooth muscle cells and proteoglycans. Most of the histologic changes already described above appear as gross plaques that are visible to the naked eye, but the fine histologic changes cannot be distinguished. Atherosclerotic lesions have been differentiated based on gross findings in the aorta. Bright yellow, minimally-raised lesions that demonstrate abundant lipid when stained with oil red O are identified as fatty streaks. The homogeneous, white, raised, firmer areas that are relatively well marked are known as fibrous plaques. fibrous plaques become dominant and progressively expand more rapidly in high-risk groups. patterns of development and growth of fatty streaks and fibrous plaques in women is similar to that in men (3).

Causal factors

Cigarette smoking

Cigarette smoking is a primary factor for majority of the cardiovascular diseases and cancers. Figure 2 reflects higher age-adjusted CAD and cardiovascular death incidence rates in men who smoke, and slightly elevated rates who quit smoking. (4)

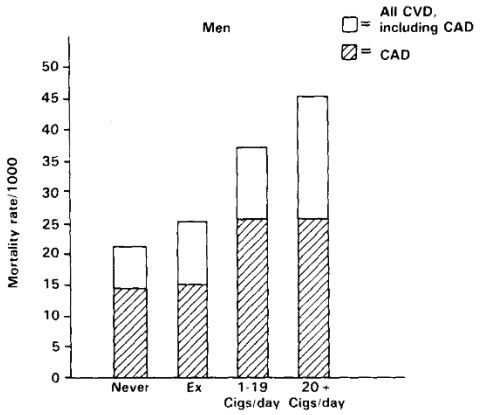

Figure 3 Age-adjusted CAD and cardiovascular death instances

Hypertension

Epidemiologic studies have shown that the risk of cardiovascular death increases with the level of blood pressure. (4)

Hyperlipidemia

Hyperlipidemia is defined as an abnormally high concentration of fats or lipids in the blood. Low-density lipoprotein (LDL) cholesterol comprises approximately 70% of total cholesterol, which is related positively to coronary diseases. However, High-density lipoprotein (HDL) cholesterol is helps fight coronary heart diseases. (4)

Low-density lipoprotein cholesterol

Cumulative LDL arterial burden is a central determinant for the initiation and progression of atherosclerotic cardiovascular disease. The lower the LDL cholesterol (LDL-C) level attained by agents that primarily target LDL receptors, the greater the clinical benefit accrued. Lowering LDL-C in individuals at high cardiovascular risk earlier rather than later appears advisable. (5)

Other factors which have a positive effect of increased atherosclerosis are Alcohol consumption, Diabetes and thrombosis.

Clinical presentation of atherosclerosis

Even as artery walls gradually thicken and stiffen, there usually are no arteriosclerosis symptoms. Even as the condition worsens into atherosclerosis, mild cases may still show no symptoms. That's why regular checkups are important. As arteriosclerosis progresses, clogged arteries can trigger a heart attack or stroke, with the symptoms such as chest pain or pressure (angina), sudden arm or leg weakness or numbness, slurred speech or difficulty speaking, brief loss of vision in one eye, drooping facial muscles, pain when walking, high blood pressure and kidney failure. (6)

Current solutions

Drugs are the first choice of treatment, even in the later stages of atherosclerosis. When drugs fail, there might be need for more aggressive strategies that include a surgical procedure. The two treatment options include angioplasty with stenting and bypass surgery. The two main treatment options for advanced atherosclerosis include angioplasty with stenting and bypass surgery.

The medical name for heart bypass surgery is Coronary Artery Bypass Graft (CABG). According to the American Heart Association, CABG involves removing a blood vessel from the chest, arms, or legs and using it to create a detour or bypass around the blockage. This allows blood to reach the heart again. Though traditionally, CABG has been performed with a cardiopulmonary bypass (on-pump CABG), CABG without the cardiopulmonary bypass (off-pump CABG) is said to have reduced number of complications. (7)

Initially, angioplasty procedures were performed without the use of a stent, a technique that is now referred as plain old balloon angioplasty (POBA). However, the outcomes were compromised due to the re-narrowing of coronary arteries due to acute vessel closure due to the dissection or elastic recoil, late vascular remodeling and neointimal proliferation (8).Elastic recoil usually occurred in 5–10% patients immediately (minutes-hours) after the procedure leading to a rebound occlusion of the artery, which often led to severe complications. (9)

Coronary stents were, therefore, developed to overcome these issues, by scaffolding the balloon-dilated artery, sealing the dissection flaps and preventing late recoil. The first coronary stent, also known as Bare Metal Stent (BMS) implanted in a human coronary artery by Sigwart et al. in 1986 named under WALLSTENT (Schneider AG). It was a self-expanding, stainless steel wiremesh structure. The use of these stents, indeed, reduced early elastic recoil and restenosis seen with POBA. (10)

However, this new technology was not without its drawbacks. These initial stents had high metallic density, resulting in a high incidence of sub-acute stent thrombosis (ST), and were bulky and technically challenging to use, resulting in frequent failure in deployment and embolization. Furthermore, these initial coronary stents, although reduced the incidence of restenosis compared with POBA, were still at a significant risk of in-stent restenosis (ISR). These technical challenges and potential complications kept the use of stents limited to the cases of acute or threatened closure or restenosis after POBA (11).

In 1993, two landmark trials, the Belgium Netherlands Stent Arterial Revascularization Therapies Study (BENESTENT) and the North American Stent Restenosis Study (STRESS), demonstrated superiority of the BMS over POBA, thus establishing coronary stent implantation as an accepted standard of care for PCI (12) (13)The costs for the initial procedure were $4,212 less for patients assigned to stenting than for those assigned to bypass surgery, but this difference was reduced during follow-up because of the increased need for repeated revascularization; after one year, the net difference in favor of stenting was estimated to be $2,973 per patient.

Current generation of BMS

There have been significant refinements in the material and design of BMS over the last few years.35 Initial stents were usually made up of stainless steel, because it is biologically inert. In recent years, cobalt– chromium alloys have superseded steel as the material of choice for stents, allowing newer stents to be designed with significantly thinner struts without compromising radial strength or corrosion resistance. A wide variety of currently used BMS, including Coroflex (B-Braun), Driver (Medtronic), Vision (Abbott Vascular) are made up of cobalt –chromium. This new platform has refined architecture with thin struts, high radiopacity, radial strength and conformability. The use of current generation of BMS, in selected (low ISR risk) patient groups could be safe and cost-effective.

However, the medium and longer term follow-up of BMS revealed as high as 20–30% incidence of ISR, due to proliferation and migration of vascular smooth muscle cells (VSMCs) within the stents. (14)

ISR may be associated with significant morbidity and mortality and the drug-eluting stents (DES) were developed to specifically address the problems of ISR encountered with BMS. (15)

Current generation of DES

Development of DES was another revolution in interventional cardiology. Various compounds targeting inflammation, platelet activation, thrombosis and VSMC proliferation were tried. Coating BMS with gold (thought to be inert), carbon (like diamond), phosphorylcholine (PC) (mimicking the cell membrane) and heparin (to prevent thrombosis), amongst many others, did not confer any benefit. Activation or antagonism of various hormonal receptors, including oestrogen, glucocorticoids and mineralocorticoids, had modest effects. (16) (17).

Drug-eluting stents (DES) reduce restenosis rates. However, there is the need for prolonged (1 year) dual antiplatelet therapy (DAT). Also, concerns have been raised regarding the higher risk of stent thrombosis, especially with the first-generation DES. Therefore, physicians and interventional cardiologists should select the use of DES or bare-metal stents (BMS), by assessing the risk of restenosis, bleeding associated with prolonged DAT and stent thrombosis in each patient (18).

Bioresorbable stents

To overcome so.me of these potential drawbacks, several companies are pursuing the development of bioresorbable scaffolds or bioabsorbable stents. Like metal stents, placement of

a bioresorbable stent will restore blood flow and support the vessel through the healing process. However, in the case of a bioresorbable stent, the stent will gradually resorb and be benignly cleared from the body, enabling a natural reconstruction of the arterial wall and restoration of vascular function. Most bioresorbable stents are made of polylactic acid, a naturally dissolvable material that is used in medical implants such as dissolving sutures These stents have controlled release of drug in parallel with biodegradation of the polymer.

Outstanding Issues

Although the bioresorbable stents have many promising advantages over metallic stents, drawbacks such as insufficient radial strength of the bioresorbable material and large strut profile of the stent need to be addressed in order to enhance the performance of the bioresorbable stents.

Innovations and potential IP opportunities

In-vivo biodegradable medical implant comprising a microstructure engineered metallic material (Patent number: **10286120**)

In-vivo biodegradable medical implants, containing at least in part at least partially fine-grained metallic materials provide a strong, tough, stiff and lightweight implant. The in-vivo biodegradable implants are used in a number of stent applications, for fracture fixation, sutures and the like. The in-vivo biodegradable medical implants enable the reduction of implant size and weight and consequently result in reducing the release of implant degradation products into the body.

Stent with rough surface and its manufacturing method (Patent number: **US20010029398A1**)

A stent is provided wherein at least an outer surface portion is roughened to a predetermined extent and wherein a drug or a therapeutic agent can be applied to said surface. This results in an improved stent, which can be manufactured at low costs and which can further avoid thrombus formation and a stenosis.

Need statement

Reducing restenosis and stent thrombosis in metal stents by incorporating antiproliferative drugs through various techniques while maintaining structural strength.

Need Criteria

The stent must have appropriate thickness for acceptable levels of blood flow, flexible stent platform with good radial strength, drug carrier for releasing antiproliferative drug. The material must be biocompatible and the design must not lead to complications such as restenosis and stent thrombosis.

Aim 1

Study and development of stents with a micro structured surface that holds the drug without a polymer and releases the active drug over a few months.

Rationale

Thin-strut stents tend to have lower profiles than thick-strut stents, making it easier to reach distally. In addition, recent clinical reports (19) (20) (21) have suggested that strut thinness may affect restenosis rates—further moving the marketplace toward thinner struts. Generally, stainless steel has been the choice of material for stents. However, cobalt alloys have been in use in the recent past. Cobalt chromium has is stronger than stainless steel, making possible thinner struts without decreasing radial strength. It is denser and more compatible with MRIs. As a result for the development of our stent Cobalt- Chromium is the primary choice.

Technical Approach

Metal additive manufacturing (AM) is an innovative manufacturing technique that can build complex and high value metal parts layer by layer using a computerized three-dimensional solid model. Powder bed fusion (PBF) is one of the most common AM techniques. It sequentially processes a powdered feedstock in thin layers and solidifies it by either a laser beam or an electron beam. PBF induces microstructural defects in the manufactured components. Micro-structured surfaces can hold the antiproliferative drug in an abluminal surface structure. As a result, the stent can be manufactured without the use of any polymer coating to hold the antiproliferative drug. These polymer-free stents offer possible shorter, dual, antiplatelet duration and also do away with possible issues of non-uniformity of drug elution from the polymer coating.

Methodology

The proposed product will be composed of three key components, including Cobalt-Chromium platform that has been modified with surface treatment resulting in a selectively micro-structured, abluminal surface. The selectively micro-structured surface allows drug adhesion to the abluminal surface of the stent without the use of a polymer or binder. The abluminal surface of the stent is texturized by displacing the metal using a micro abrasion process resulting in a selectively micro-structured surface. The resulting crevices of this selectively micro-structured surface allow a significant portion of the drug to wick into the stent surface thereby providing a means for anchoring the drug. One potential advantage of this system lays on the possibility of using different drug concentrations and combinations of different agents. The operator may increase (or decrease) the amount of antiproliferative drug according to patient and lesion complexity.

Expected results

The composition can be modified such that the drug will be released from the stent as per the requirement which varies with the patient. This product will aim at eliminating any polymer coating which would reduce the overall thickness of the stent and reduce the elastic recoil which leads to restenosis.

Aim 1

To study the effect of various micropore shapes on the surface of metals to determine the drug holding capacity to eliminate the use of polymer coating.

Rationale

Materials such as stainless steel and cobalt chromium can be used to create a slotted-tubular microstructure on the surface capable of carrying drugs. Majority of the AM processes involving metal additive manufacturing tools have feature-size resolutions of greater than 100 µm, which is too large to precisely control the geometrical and dimensional aspects of the parts they produce. Various microstructural shapes can be made using a µ-SLS uses a 3W CW laser (532nm) which has a resolution of 1 µm (22). This process helps generate shapes such as slotted tubular surfaces, hexagonal slots and rectangular slots which would hold the drug in the stent.

Technical Approach

As mentioned earlier, a µ-SLS uses a 3W CW laser (532nm) which has a resolution of 1 µm, can be used to create different microstructural shapes in the metal stent. The drug can be inserted into the stent with ultrasonic coating. The process is estimated around 10 minutes.

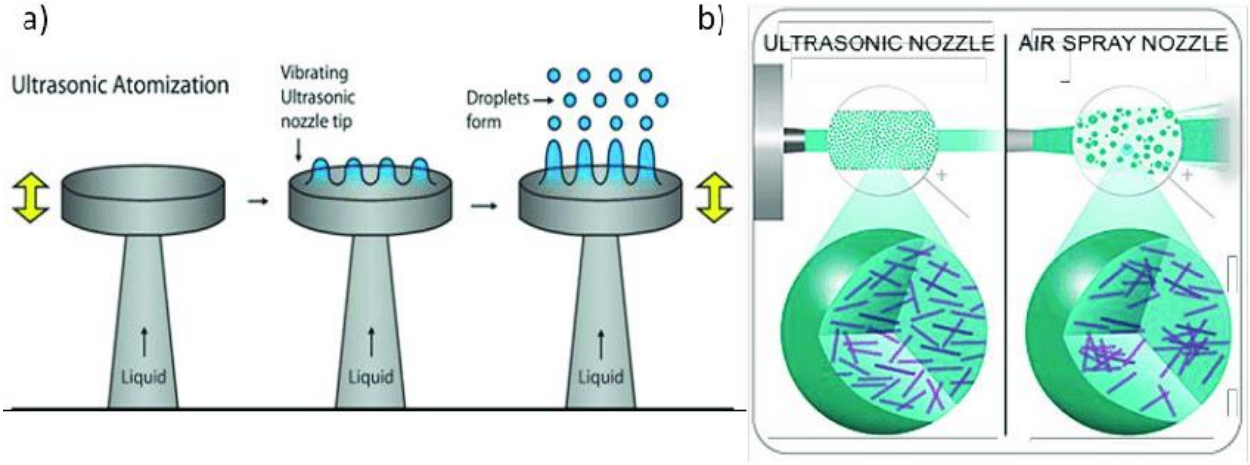

Figure 4 Ultrasonic coating process

Methodology

Drug diffusion rate in various microstructural shapes can be determined experimentally and can be mathematically modelled. Therefore, a relationship between microstructural shape depending on the area covered, drug holding capacity and its diffusion rate can be calculated. Also, structural strength of all the resulting stents can be determined and the best stent would be selected.

Expected Results

The resulting process should be fast to enable for mass production. Different shapes would result in different diffusion rates and as a result, the microstructural shape can be varied depending on the patient requirements. In addition, the product should hold the required structural strength for all the shapes.

Commercialization Plan

Market and Customer

The cardiovascular stents market is expected to reach $13.1 billion by 2025, up from $7.8 billion in 2017, according to projections from Fortune Business Insights. Fortune Business Insights' most recent report on CV stents estimates a compound annual growth rate of 6.6% through 2025—an increase driven largely by updated drug-eluting systems (DES) and the development of bioresorbable stents.

Competitors

Some of the main key players in the market are Biotronik SE and Co. KG, Cardinal Health, Cook R. Bard Inc., MicroPort Scientific Corporation, Terumo Corporation, Braun Melsungen AG, Abbott, Boston Scientific Corporation, Medtronic. Rising geriatric population and their vulnerability towards various diseases are creating the need for medical aids such as coronary stents. Rising prevalence of cardiovascular diseases will also augment the market during the forecast period.

Value proposition and Competitive advantages

The proposition aims at solving the above identified gaps in two stages. In stage I, the micro-structed stents can be developed using Additive Manufacturing techniques which can provide great structural properties and the product can be altered depending on the requirements for the patient. The product can be manufactured in bulk and would therefore, be of low cost. The second stage aims to look at the shape of various microstructures possible and their effects on drug delivery and structural strength. Though more research is required to determine the drug delivery rate possible in various geometries, the benefits of the possible product would truly revolutionize the stent industry.

Pathway to regulatory approval

FDA Guidance requirement

Criterias such as Dimensional Verification, Delivery, Deployment, and Retraction, Balloon Rated Burst Pressure (Balloon Expandable Stents Only), Balloon Fatigue (Repeat Balloon Inflations; Balloon Expandable Stents Only), Balloon Compliance (Stent Diameter vs. Balloon Pressure; Balloon Expandable Stents Only), Balloon Inflation and Deflation Time (Balloon Expandable Stents Only), Catheter Bond Strength, Tip Pull Test, Flexibility and Kink Test, Torque Strength, Coating Integrity Stent Securement for Unsheathed Stents are needed to be fulfilled for approval from the FDA.

Premarket Approval (PMA) for ABSORB GT1 BIORESORBABLE VASCULAR SCAFFOLD (BVS) SYSTEM was granted for ABBOTT VASCULAR INC. This device is indicated for improving coronary luminal diameter in patients with ischemic heart disease due to de novo native coronary artery lesions >=2.5 mm to <=3.75 mm in diameter in lesions <=24 mm in length.

References

1. *"A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association." .* Stary, Herbert C., et al. 1992, Vol. 85.1.

2. *Atherosclerosis.* Pahwa R, Jialal I. 2019.

3. Pahwa R, Jialal I. et al. Atherosclerosis. s.l. : StatPearls Publishing, 2019.

4. *"Epidemiology of atherosclerosis: an updated overview.".* Criqui, Michael H. s.l. : The American journal of cardiology, Vol. 1986. C18-C23..

5. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. *Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Pane.*

6. Rathore, Saif S., et al. "Characterization of incident stroke signs and symptoms: findings from the atherosclerosis risk in communities study." 2718-2721. 2002.

7. *"On-pump versus off-pump coronary-artery bypass surgery.".* (Shroyer, A. Laurie, et al. 361-19, s.l. : New England Journal of Medicine, 2009. 1827-1837.

8. *Mechanisms and prevention of restenosis: from experimental models to clinical practice.* Bauters C, Meurice T, Hamon M et al. 835-46, s.l. : Cardiovasc Res , 1996.

9. *Platelets and restenosis.* (Chandrasekar B, Tanguay JF. et al. 555-62, 2000.

10. *Incidence, predictors, and management of acute coronary occlusion after coronary angioplasty.* de Feyter PJ, de Jaegere PP, Serruys PW. Am Heart J et al. 127:643–51, 1994.

11. *Angiographic follow-up after placement of a selfexpanding coronary-artery stent.* Serruys PW, Strauss BH, Beatt KJ et al. 324:13–7, s.l. : N Engl J Med, 1991.

12. *A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. .* Serruys PW, de Jaegere P, Kiemeneij F et al. 331:489–95, s.l. : BENESTENT study group, Vol. 1994.

13. *A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease.* Fischman DL, Leon MB, Baim DS et al. N Engl J Med 1994 and 331:496–501.). s.l. : Stent restenosis study investigators.

14. *Patterns and mechanisms of in-stent restenosis.* (Hoffmann R, Mintz GS, Dussaillant GR et al. 94:1247–54, s.l. : A serial intravascular ultrasound study, 1996.

15. *Bare metal stent restenosis is not a benign clinical entity.* Chen MS, John JM, Chew DP et al. 151:1260–4, 2006.

16. *Contribution of endogenous glucocorticoids and their intravascular metabolism by 11 beta-HSDs to postangioplasty neointimal proliferation in mice. .* Iqbal J, Macdonald LJ, Low L et al. s.l. : Endocrinology, 2012, Vols. 153:5896–905.

17. *Therapeutic manipulation of glucocorticoid metabolism in cardiovascular disease.* Hadoke PW, Iqbal J, Walker BR. Br J Pharmacol. 156:689–712, 2009.

18. *Predicting the restenosis benefit of drug-eluting versus bare-metal stents in percutaneous coronary intervention.* Evaluation of: Yeh RW, Normand SL, Wolf RE et al. s.l. : Circulation, 2011, Vols. 1557–1564.

19. *In-stent restenosis in small coronary arteries: impact of strut thickness.* Briguori C, Sarais C, Pagnotta P, Liistro F, Montorfano M, Chieffo A, Sgura F, Corvaja N, Albiero R, Stankovic G, Toutoutzas C, Bonizzoni E, Di Mario C, Colombo A.

20. *A. Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO Trial),.* Kastrati A, Mehilli J, Dirschinger J, Dotzer F, Schühlen H, Neumann FJ, Fleckenstein M, Pfafferott C, Seyfarth M, Schömig.

21. *Intracoronary stenting and angiographic results: Strut thickness effect on restenosis outcome.* Pache J, Kastrati A, Mehilli J, Schühlen H, Dotzer F, Hausleiter J, Fleckenstein M, Neumann FJ, Sattelberger U, Schmitt C, Müller M, Dirschinger J, Schömig. 2003.

22. *"Design of a micro-scale selective laser sintering system." .* Roy, Nilabh K., Chee S. Foong, and Michael A. Cullinan. s.l. : Annual International Solid Freeform Fabrication Symposium, 2016.

24. *"Intelligent functionally graded material: bamboo.* Nogata, Fumio, and Hideaki Takahashi. ". 743-751, s.l. : Composites Engineering, 1995.

25. *.(Welcher, F. J., Ed. Standard Methods of Chemical Analysis and Nostrand:, Van. NJ : Princeton,, 1963.*

26. Elvers, B., Hawkins, S. and Shulz, G., Eds. Ullmann's Encyclopedia of Industrial Chemistry. Weinheim : s.n., 1991.

27. Bamboo-Polylactic Acid (PLA) Composite Material for Structural Applications. Materials (Basel). Pozo Morales A, Güemes A, Fernandez-Lopez A, Carcelen Valero V, De La Rosa Llano S. 10.3390/ma10111286, 2017.

28. Biodegradability evaluation of polymers by ISO 14855-2. . Funabashi M, Ninomiya F, Kunioka M. 3635–3654., Aug 2009 : Int J Mol Sc. 10.3390/ijms10083635.