Review Article

An Overview on Coronary Artery Disease and Cardiovascular Stents

ABSTRACT

Coronary artery disease is commonly called coronary heart disease, a condition with inadequate supply of blood and micronutrient to heart due to narrowing of arteries. Generally, symptoms are not seen in early stages but as disease progress common signs such as discomfort in chest, shortness of breath, tiredness and irregular heartbeats are detected. Primarily, CAD was one of the uncommon causes of death in the start of 20th century. But this scenario was changed from mid 1960s as peaks were observed in CAD deaths. At present, CAD is leading cause of death worldwide, though there is significant decline. However, there are treatments available for this medical condition such as angioplasty and stent placement. In this review, we present a detail study on diagnosis, risk factors, potential treatment options using different stents and their availability as well as relevant benefits. Furthermore, the future prospects of stent technology are also discussed.

Keywords: *Systemic review, Coronary artery disease, Diagnosis and Treatment, Stents, Bare metal stents, drug eluting stents, Bioresorbable and degradable stents.*

ABBREVIATION

CAD- coronary artery disease
WHO- World health organization
PTCA- Percutaneous transluminal coronary angioplasty
DPD- Distal protection device
BRS- Bare metal stents
DRS- Drug eluting stents
RBS- Resorbable and biodegradable stents
FDA- Food and drug administration

1. INTRODUCTION

Coronary artery disease (CAD) is characterized by formation of plaque in the wall of arteries that is pivotal for blood supply. This condition of cardiovascular disease occurs through process called atherosclerosis (or 'atheroma'), a slow progressing condition which perhaps begin in early life and cause symptoms in later stages. The mode of atheroma formation involves deposition of lipids, collagen or cholesterol and proliferation of muscle cells that builds up as plaque inside arteries. Initially, this reflects in loss of elasticity and thickening of blood vessels specifically those closer to curvatures or branches. Though there is advancement in detection and treatment, CAD is estimated to account for highest morbidity. Looking at statistics, CAD is most diagnosed and responsible for higher mortality rate in comparison to other human diseases. Globally, morbidity rate is around 17.9 million men and women each year and accounts for 1/3rd of deaths worldwide[1]. In addition, according to WHO, India contributes around $1/5^{th}$ of these cases mainly in younger population. Various reports have estimated that in 2016, India had around 24 million patients suffering from CAD [2,3]. Besides, there is no organized data collection approach regarding CAD for Indian sub-continent and also most of the demises occurs at home without perceiving the reason behind it. However, there has been significant reduction, approximately 30% of CAD

deaths around the world through contribution of early diagnosis and engineering therapies but still certain challenges have to be addressed to improve patient's life expectancy especially in developing countries [1].

In general, human heart is located in thoracic cavity with an average size of 9cm length, 8cm width, 6cm thickness and weighs around 250-300g in a grown-up. The basic structure mainly constitutes four chambers: right and left atrium/ventricle, guarded by various valves [4]. This organ functions by circulating blood to other parts of the body through vascular structures such as arteries and veins. Importantly, these arteries are right coronary artery and two on left side: left anterior descending artery (LAD) and left circumflex artery (LCX) that lined-up surface with approximate sizes of 2.8cm length, 3.1mm diameter and ~1.9cm length, 4.6mm diameter respectively [4,5]. In the entire process of circulation, coronary arteries lining up walls of heart and veins have imperative role in providing and distributing oxygen-rich blood to and from heart muscles. But in case of CAD patients, some have reported diameters of arteries were 2.80 ±0.37 mm for average, indicating remodeling of arteries [5].

Such accumulating evidences suggest that obstruction of these hallow tubes ultimately results in inadequate supply of blood to meet metabolic requirements of heart muscles. If this persist and prolonged, then subsequently tissue dies and leads to serious conditions as 'heart attack' [5]. Therefore, looking at early signs of CAD includes clinical manifestations such as angina (chest pain) due to low blood supply), abnormal heart beats and difficulty in breathing is significant.

2. RISK FACTORS FOR CAD

There are multiple risk factors for coronary artery disease which can be classified as controllable and non-controllable factors. The factors that can enhance the chances of disease but are modifiable are blood pressure, balanced diabetes, obesity or unbalanced weight, stress, dearth of physical activity, extensive stress and unhealthy lifestyle such as excess alcohol consumption or smoking. On other hand, certain other factors include genetic heredity or family history, obstructive sleep apnea (failure of upper airways during sleep) and metabolic syndromes [6]. In addition, these risk factors advance with age and many studies have indicated that men are more prone to this disease [7]. Therefore, it is significant to understand these factors and take precautionary measures to prevent the likelihood of developing CAD.

3. DIAGNOSIS OF CAD

For coronary artery disease, narrowed or blocked arteries are being diagnosed via different tests. Primarily, an electrocardiography is done which indicates irregular heart beat and electrical activity. Also, exercise and pharmacological-stress tests, where individuals are asked to walk on treadmill or drugs are induced to enhance heart rate to analyze their heart working condition. These allow to identify chest pain and artery blockage. Other basic test which can be performed are echocardiogram, blood test (for cholesterol, glucose, lipo-proteins and other reactive proteins), cardiac catheterization [8]. In addition, some advanced imaging techniques such as CT (computer tomography) which can scan the heart to detect calcium deposits and provide image of blocked coronary vessels or nuclear imaging where radio-active tracers are administered to get better images of heart [8,9]. All these tests assist medical personnel to detect early signs of heart attack and take necessary precautionary steps.

4. TREATMENT

Available treatment options for CAD are angioplasty in association with endovascular stent placement. Angioplasty or PTCA (percutaneous transluminal coronary angioplasty) is less invasive approach to widen arteries congested due to plaque deposition and utilize stents to re-establish blood flow for circulation [10]. Importantly,

this stent procedure is recommended as medical necessity only if patient have 70% blockage of an artery with symptoms. Since past 25 years, use of this technique has steadily expanded and preferred as alternative approach to bypass surgery, particularly in individuals with one-vessel problem. [11]

The technological development in this field have led to improved safety and longevity of PTCA. For example, use of stents with drug elution or distal protection device (DPD) has enhanced clinical outcomes. The success rate is 90 percent for non-occluded (not closed) and around 70 percent for occluded (completely closed) arteries [12]. The expense of overall procedure on average ranges between Rs 40,000- Rs 50,000 in government hospitals like AIIMS which might increase with private hospitals on economical view [13].

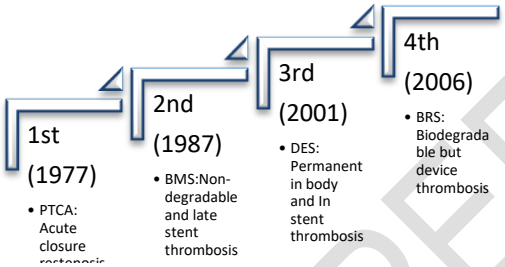

Figure 1: Represents evolution of stents

So, stent is a small medical device with a structure resembling hallow mesh and are often positioned permanently inside affected site during PTCA to regain normal blood flow to cardiac muscles. Looking at their evolution, in 1977, first angioplasty technique was executed in blocked vessels (first revolution), which led to new era of coronary disease [14]. Then in 1986, first stent composed of stainless steel was implanted in coronary artery to function as scaffold through preventing vessel closure by Puel Dudley and Ulrich Sigwart. Bare metal stents were regarded as second revolution of cardiac therapies. In 1994, Palmaz and Richard Schatz were accredited for development of first FDA(US) approved expandable balloon stent. Later in 2003, a novel approach was discovered in order to overcome occurrences of restenosis, which was a combination of polymer-drug eluting stents (DES) and considered it as third revolution [14,15]. At present, biodegradable or resorbable stents are being researched to overcome shortcomings associated with previous materials.

5. TYPES OF STENTS

Based on design, materials used and thickness of strut, stents are classified as follows:

5.1 Bare Metal Stent (BMS)

BMS are first generation stents, which are traditionally employed as therapeutic procedure in coronary artery disease (CAD). These are first clinically licensed cardiac stent arranged in tiny tubular-segmental fashion, composed of 316L SS (stainless steel) alloy such as iron, nickel, chromium, molybdenum and other materials like nitinol. Usually, their diameter ranges within 2.5-4.0mm and are non-degradable in the body. [14,16]

The dimensions of these metallic stents are estimated to be 80um thickness, 90um width and opening size of 4.5mm with radial force around 25psi. In addition, their design permits up to 4.6mm expansion across branches for effective bifurcation stenting. Looking into their physical characteristics stainless-steel (SS) stents have high elasticity and tensile strength which was adequate enough to prevent recoiling but was limited due to dearth of radio opacity and deliverability [17]. However, an attempt was made to address this shortcoming with addition of gold to SS stents but unfortunately due to thicker strut it was not compatible. In addition, other materials like cobalt-chromium, platinum-chromium are designed with lesser thickness as well as high radial strength and radio-opacity. This has improved clinical response by reducing restenosis (re-narrowing of arteries). [14,16]

Limitations: Though the non-biodegradable bare metal stent (BMS) was capable of preventing early coagulation, there were certain complications including long-lasting inflammatory responses or hyperplasia

reflecting late thrombosis after implantation of stent [14,18]. These are certain clinical consequence but it does reduce abrupt artery closure. However, these issues of metal stents are being addressed using advanced combination of materials with appropriate design.

Some commercially available bare metal stents include for stainless steel: GRAFTMASTER marketed by company Abbott Vascular, which cost approximately Rs 8319; cobalt chromium stents: some examples are NEXGEN (Meril life science), INTEGRITY (Med Tronic) and TREKTM (Abbott vascular), charged about Rs 7000-Rs 8000; platinum-chromium stents: example OMEGA-BMS (Boston Scientifics). The premium prize of metallic stenting is expected to be Rs 8300 and might vary based on components [19,20].

5.2 Drug Eluting Stents (DES)

DES are tiny mesh like tubular structure which can be categorized into metallic and polymer stents coated with drugs such as immune-suppressants to decrease immune rejection or anti-cancer drugs to regulate cellular propagation [21]. This has emerged as effective method to encounter incidences of re-narrowing or inflammation as consequence of bare metal stent placement. Mostly, DES are recommended for coronary disease, when the abrupt arteries have lesion >15mm or calibre <3mm. These implants are permanent and non-biodegradable, and were successfully able to promote enhanced blood flow and vasomotion (rhythmic modulation of vessels) [22,23].

DES are constructed with metals like stainless steel alloy or platinum-chromium to provide framework in the form of mesh-tubular structure and a polymer matrix bound with drug coated on to stent wire, which is slowly released into tissues. The polymer is composed of synthetic materials: EVA (polyethylene-vinyl acetate), poly-n-butyl methacrylate mixture or gelatin coacervate (films) and PCL [poly(lactide-co-polycaprolactone)], successfully used till date [17,22]. A variety of drugs are deployed such as paclitaxel or Everolimus which are chemotherapeutic agent for cancer; rapamycin or tacrolimus immunosuppressor medicines; dexamethasone, corticosteroids to minimize inflammation [24]. The mode of action involves elution of embedded drug from matrix through diffusion into surrounding tissues at different rates, depending on number of polymer layers applied on the device. This can be regulated by engineering the design of matrix polymer drug system [25].

The first drug eluting stents was sirolimus eluting stent which became clinically available in 2002. This was marketed by cordis under brand name CYPHER. Another example is Taxus by Boston scientific which is a paclitaxel eluting stents for CAD [14]. These improved the clinical outcomes and reduced restenosis. But there are some debates regarding their safety due to their potential for late-thrombosis (blood clots blocking vessels), particularly when dual anti-platelet therapies are stopped [24]. However, there is emergence of second-generation of drug eluting stents such as Everolimus eluting stent and Zotarolimus-eluting stents. A number of studies have evinced the superiority of second-generation DES over Taxus in terms of restenosis and other threatening events [25]. Nonetheless, more studies need to be performed for definitive conclusion.

Limitations: However, certain studies have suggested a slight rise in blood clots post implantation causing heart attack which might be risky. The cause and significance of in-stent coagulation is still a controversy. Also, its efficacy along with safety over longer duration is still concerned [26]. This late-stent condition might not negate other advantages of drug eluting stent outcomes.

Some examples of preferred DES products that are available in market are: XIENCE XPEDITION (Abbott Healthcare) – Everolimus-Eluting stent costs Rs 30,080; PROMOUS PREMIER (Boston Scientific)- Everolimus-eluting platinum chromium coronary stent and costs Rs 30,080;

BIOMIME (Meril life science) – sirolimus eluting stent that costs Rs 22,500; ONYX (India Medtronic) - Zotarolimus-Eluting Coronary Stent, charge about 30,050. There are other products developed and marketed by multiple companies at different cost. However, there is differences in price between DES and BMS, which comparatively holds drug eluting stents more expensive [19,20].

5.3 Resorbable and Biodegradable Stents (RBS)

RBS is fourth revolution for treating coronary artery disease. Unlike other two classes, these stents ultimately degrade and removing implant materials might cause a sever clotting event. RBS acts temporarily as supporting material to vessels for 4-5 months. By then, disrupted artery will be healed. This reflects potential advantage of RBS i.e., restoration of vascular tissues which maintains standard integrity of vessels because degradation of foreign materials permits vascular-reactivity with positive artery remodeling.[15]

These biodegradable stents are constructed using polymers for example materials synthesized from caprolactone or lactic acid, PGA (poly glycolic acid), polyesters like PCL (poly-ε- caprolactone), PLLA (poly L-lactic acid) and other co-polymers [27]. Recent studies in this field suggest RBS are more versatile in succeeding therapies and no intervention are needed during clinical diagnosis (like imaging: CT or CMR, cardiac magnetic resonance). In addition, there are on-going research on utilization of metallic components (iron, manganese or zinc based) in RBS. There are many variants of biodegradable stents which are in clinical stage [28].

In 2016, ABSORB GT1 BVS (bioresorbable vascular scaffold system) was first clinically approved RBS stent and result data showed promising outcomes. One main advantage of this stent was its capability to degrade over time, there by leaving no foreign objects inside the body and eventually promote vasomotion as well as minimize device-thrombosis compared to other stents [27,29]. But at present it's been withdrawn from commercial use.

Limitations: Despite certain clinical advantages, RBS has not addressed all glitches associated with other class for cardiac interventions. RBS require improvements in strut thickness with good mechanical stability, appropriate degradation kinetics and prevent sever post-implantation side effects i.e. (in-stent) restenosis and thrombosis [27,30].

6. CONCLUSION

Stent technology has encountered rapid evolution with continual advancements of coronary interventions. Looking at novel materials and scaffold fabricating approaches, it can be concluded that we have effectively addressed the issues of acute vessel obstruction to good extent, utilizing bare metal stents and drug eluting stent. In India, NPPA (National Pharmaceutical Pricing Authority) has prescribed the prices for these stents which spans from Rs 8,261-Rs 30,080. Sometimes the ceiling price of these stents can be revised to more affordable cost. These two classes of stents are everlasting and there's about 2-3% risk of re-narrowing which generally occurs within 6-9 months. Such incidences are treated with new stent replacement. However, several innovative designs of these stents have enhanced radial strength and overall profile of device for successful procedure. In contrast to metallic and drug eluting stent, biodegradable scaffolds (BRS) which resorb might be advantageous. But, at present only one FDA (food and drug administration) approved BRS could enter market, which is now discontinued on safety grounds. Despite certain clinical disadvantages, stent devices have been successfully implanted and showed positive outcomes with improvement in patients' life. Most of these devices were able to reconcile the patency of coronary vessels. Economically, basic stents such as bare metal or drug eluting stents are at more affordable expense in India compared to other countries and

around 13.4 million people every year are treated globally.

7. FUTURE SCOPE

This field has demonstrated various advancements, since the discovery of PTCA (or angioplasty). Even though, improvements in stent design and construction are required. At present, various research on development of synthetic stent grafts by engineering their surface with bio-active ingredients to resolve aggregation and muscle cell propagation is conducted. Especially promotion of endothelization of stents, which in turn assist in preventing bacterial infections post-implantation are being studied. Future work of drug eluting stent technology, mainly focused on optimizing outcomes with unique designs that can regulate release of drug at particular time in required rate. In context of design, ultra-thin stents are being explored of ~100µm thickness to mitigate device thrombosis and ease the process of implantation. Finally, the future strategies for innovation of biodegradable stents include enhancement of biocompatibility, mechanical stability, degradation kinetics, geometry, as well as flexibility to perform multiple functions. Furthermore, a combination of present stenting technology along with sensors are researched in the context of coronary disease. The future of stents is significantly influenced by biosensors which can modify the whole concept of stenting. So overall, stents have improved life expectancy and future is anticipated to be more promising.

REFERENCES

1. Cassar A, Holmes DR, Rihal CS, Gersh BJ. Chronic coronary artery disease: Diagnosis and management. Mayo Clin Proc. 2009. p. 1130–46.
2. Sreeniwas Kumar A, Sinha N. Cardiovascular disease in India: A 360 degree overview. 2020; Available from: https://doi.org/10.1016/j.mjafi.2019.12.005
3. Rao M, Xavier D, Devi P, Sigamani A, Faruqui A, Gupta R, et al. Prevalence, treatments and outcomes of coronary artery disease in Indians: A systematic review. Indian Heart J. Elsevier B.V.; 2015;67:302–10.
4. Katz A. Physiology of the Heart. 2010 [cited 2022 Aug 20]. Available from: https://books.google.com/books.
5. Raut BK, Patil VN, Cherian G. Coronary artery dimensions in normal Indians. Indian Heart J. Elsevier; 2017;69:512.
6. Heart RH-H views: the official journal. Risk factors for coronary artery disease: historical perspectives. ncbi.nlm.nih.gov.2017.
7. Kr Malakar A, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. 2019;
8. Nelson AJ, Ardissino M, Psaltis PJ. Current approach to the diagnosis of atherosclerotic coronary artery disease: more questions than answers. Ther Adv Chronic Dis. SAGE Publications Ltd; 2019;10.
9. Sdogkos E, Xanthopoulos A, Giamouzis G, Skoularigis J, Triposkiadis F, Vogiatzis I. Diagnosis of coronary artery disease: potential complications of imaging techniques. Acta Cardiol. Taylor and Francis Ltd.; 2022;77:279–82.
10. Castaneda-Zuniga WR, Formanek A, Tadavarthy M, Vlodaver Z, Edwards JE, Zollikofer C, et al. The mechanism of balloon angioplasty. Radiology. 1980;135:565–71.
11. Dotter CT. Transluminal angioplasty: A long view. Radiology. 1980;135:561–4.
12. Yu Jia Z, Sun Song Y, Jon Sheen J, Goo Kim J, Hee Lee D. Endovascular recanalization of symptomatic non–acute intracranial artery occlusion: Procedural and mid-term clinical outcomes in the anterior circulation. Interv Neuroradiol. 2019;
13. Stents cheaper, but not all get benefit | India News - Times of India. [cited 2022 Aug 19]. Available from: https://timesofindia.indiatimes.com.
14. Schmidt T, Abbott J. Coronary Stents: History, Design, and Construction. J

Clin Med. 2018;7:126.
15. Hu T, Yang C, Lin S, Yu Q, Wang G. Biodegradable stents for coronary artery disease treatment: Recent advances and future perspectives. Mater Sci Eng C. Elsevier B.V; 2018;91:163–78.
16. Lau KW, Johan A, Sigwart U, Hung JS. A stent is not just a stent: Stent construction and design do matter in its clinical performance. Singapore Med. J. 2004.
17. J. Guerra A, Ciurana J. Stent's Manufacturing Field: Past, Present, and Future Prospects. Angiography. IntechOpen; 2019.
18. Bangalore S, Toklu B, Amoroso N, Fusaro M, Bmj SK. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment. 2013.
19. Wadhera P, Alexander T, Nallamothu BK. India and the coronary stent market getting the price right. Circulation. Lippincott Williams and Wilkins; 2017;135:1879–81.
20. Hospital A. Cardiac Stents Pricing to patient - Apollo Hospitals. Apollo Hosp. Website. 2017 [cited 2022 Aug 20]. Available from: https://www.apollohospitals.com/departments/heart/stent-prices-disclosure/
21. Lüscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, et al. Drug-eluting stent and coronary thrombosis: Biological mechanisms and clinical implications. Circulation. 2007. p. 1051–8.
22. Stents DC. Drug-Eluting Coronary-Artery Stents. 2013;
23. Maisel WH, Laskey WK. Drug-eluting stents. Circulation. 2007;115.
24. Hoeven B Van der, Pires N, … HW-I journal of, 2005 undefined. Drug-eluting stents: results, promises and problems. Elsevier. 2007.
25. Martin D, physics FB-M engineering. Drug-eluting stents for coronary artery disease: a review. Elsevier. 2011.
26. Sim DS, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, et al. Effectiveness of drug-eluting stents versus bare-metal stents in large coronary arteries in patients with acute myocardial infarction. J Korean Med Sci. 2011;26:521–7.
27. Tabraiz Alam MS, Ansari AQ, Urooj S, Aldobali M. A review based on biodegradable and bioabsorbable stents for coronary artery disease. Procedia Comput Sci. Elsevier B.V.; 2019;152:354–9.
28. Bourantas C V., Zhang Y, Farooq V, Garcia-Garcia HM, Onuma Y, Serruys PW. Bioresorbable scaffolds: Current evidence and ongoing clinical trials. Curr Cardiol Rep. 2012;14:626–34.
29. Zong J, He Q, Liu Y, Qiu M, Wu J, Hu B. Advances in the development of biodegradable coronary stents: A translational perspective. Mater Today Bio. 2022;16.
30. Zhu J, Zhang X, Niu J, Shi Y, Zhu Z, Dai D, et al. Biosafety and efficacy evaluation of a biodegradable magnesium-based drug-eluting stent in porcine coronary artery. Sci Reports 2021;11:1–12.