RESEARCH

Review of Contemporary Coronary Artery Stents and Future Developments

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ABSTRACT

Cardiovascular diseases (CVDs), including coronary artery diseases (CADs) are the leading cause of morbidity and mortality worldwide. CAD often relates to plaque build-up in the arteries of the heart. The optimal treatment of CAD still remains a topic of debate as several trials scrutinizing efficacy of the two widely accepted approaches in CAD treatment namely, Percutaneous Coronary Intervention (PCI) with stenting, and Coronary Artery Bypass Grafting (CABG), indicate an association of increased rate of repeat vascularisation with PCI and a major increase in the rate of stroke with CABG. Previously, balloon angioplasty was also recommended tool for CAD treatment, however, balloon angioplasty no longer is a preferred choice due to higher incidence of arterial recoil, coronary dissection and neointima formation, ultimately leading to abrupt vessel closure and clinical restenosis. Although with the advent of PCI, use of coronary stent significantly reduced the chances of arterial recoil and stabilizes vascular dissections, the issues of neointimal thickening and in-stent restenosis still need to be addressed. To overcome this, coronary stents have evolved drastically in design, structure and material. In recent times, drug eluting stents have emerged as an effective approach to combat these complications associated with stent implantation. Therefore, the aim of this review is to discuss the recent developments in the field of coronary stents, including a detailed description of the different types of metal stents and the adverse outcomes occurring due to metal incompatibility. This review also provides insights on stent incompatibility and the latest advances made to overcome stent metal incompatibility problems.

KEYWORDS: Coronary artery bypass grafting, Drug-eluting stent implantation, polymeric biomaterials.

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1. Introduction

Cardiovascular diseases (CVDs) are the leading cause of mortality and accounted for 17.6 million deaths worldwide in 2017 according to the WHO report. The American Heart Association (AHA) has projected this number to reach 23.6 million by 2027. With such a high mortality rate associated with CVDs due to reasons varying from genetics to unhealthy lifestyles, extensive research has been going on for decades to treat and prevent CVDs. Coronary artery disease (CAD) develops when the blood vessels such as the coronary artery are damaged due to cholesterol deposition in the form of plaque, ultimately leading to atherosclerosis [1]. Apart from drugs like beta-blockers, cholesterol modifiers, aspirin, and ACE inhibitors; coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI) with stent placement, or angioplasty procedures are carried out to restore the blood flow in atherosclerotic patients [2], with CABG considered as the conventional treatment of choice. However, improper cardiac rhythm, blood clots, risk of bleeding at the site of grafting, post-cardiotomy, and increased mortality are the observed limitations associated with CABG. Over time, PCI with stenting has emerged as a widely accepted strategy considering its beneficial outcomes. The use of stents is a major choice of treatment in advanced conditions of CAD and atherosclerosis.

Stents are tiny mesh-like tubes made up of medical-grade material that holds the clogged artery wide open, restoring blood flow. The design of stents has drastically evolved from Balloon Angioplasty in 1977 to bioresorbable, drug-eluting, and polymer-eluting stents [3]. The initial stents used, namely the balloon angioplasty and the bare-metal stents (BMS) caused platelet aggregation, acute and sub-acute thrombosis. leading to restenosis. Moreover, balloon angioplasty had an additional disadvantage of elastic recoil, leading to the closure of the circulatory pathway, which further led to acute myocardial infarction, and thus patients requiring CABG. This has made scope for further development in the existing stents [4]. Many clinical trials have been conducted to study the effects and benefits of stents. To date more than 800 completed clinical trials on the use of stents in CAD are registered with clinicaltrials.gov, highlighting the importance of stents in CAD treatment [5]. In this review, we aim to highlight the advances in the field of coronary artery stenting (CAS) that provide a beneficial scope for CAS as a replacement tool for CABG.

2. Coronary Artery Bypass Grafting (CABG) vs Coronary Artery Stenting (CAS)

Numerous studies, including randomized controlled trials and meta-analysis, comparing the safety and efficacy of CAS with CABG have been published in the last few decades. These studies concluded that CABG was associated with lower rates of major adverse cardiac or cerebrovascular events as compared to PCI with stenting thus remaining the choice of treatment for patients with CAD.

In the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, the investigators scrutinized the efficacy of PCI with drug-eluting stents compared with CABG in patients with complex coronary disease (n=1800), by randomizing patients to receive either PCI or CABG (in 1:1 ratio) and lead to the conclusion that at 12 months, PCI was found to be associated with higher rates of major adverse cardiac or cerebrovascular events (17.8% vs 12.4% for CABG; P=0.002) with an increased rate of repeat revascularization (13.5% vs 5.9% for CABG; P<0.001), the rates of death and MI were found to be similar among the two groups, however, CABG

was found significantly associated with a higher risk of stroke (2.2% vs 0.6% with PCI; *P*=0.003) [6].

A diabetic substudy of patients with multivessel CAD comparing the group of patients who underwent CABG with those receiving stent showed higher rates of repeat vascularisation associated with stenting at 12 months (14.3%), thus favouring CABG. Also, no significant difference in rates of death, MI, and cerebrovascular events were observed between the two groups [7].

Other studies comparing risk-associated survival rate showed mortality benefits with CABG as compared with PCI. Recent studies comparing the outcomes in patients with CAD who underwent CABG vs the ones who underwent PCI with second-generation drug-eluting stents (n=34819), after 2.9 years follow-up, lead to the outcome that PCI with everolimus-eluting stent and CABG had similar rates of risk of death (3.1% per year and 2.9% per year, respectively), with a higher risk of MI with PCI than CABG (1.9% per year for PCI vs 1.1% per year for CABG), a higher repeat vascularisation with PCI than CABG (7.2% per year for PCI vs 3.1% per year for CABG) and an increased risk of stroke with CABG than PCI (1.1% per year for CABG vs 0.7% per year for PCI) [8].

However, most trials comparing PCI with CABG are older than the current technology medical therapy and even the skill sets of interventional cardiologists these days. Older trials may have been limited by their use of first-generation drug-eluting stents that reduced the rate of restenosis but also lead to the increased rate of stent-related thrombosis events. In the present times, various developments and advancements in stenting have shown to have beneficial outcomes with PCI, thereby reducing the rates of death, MI, restenosis, and stent thrombosis. Additionally, the gap in revascularization rate which is mostly designated as superior in CABG vs PCI has been dramatically reducing since the advent of technologically advanced types of stents.

3. Types of coronary stents

3.1. Bare metal stents (BMS)

The first-ever stent to be used for coronary stenting was the BMS [9]. The BMS stents have been refined as per the requirements. When first made, they were made of 316L stainless steel, nitinol coils, or wire coils of different designs possessing the capability of self-expansion/balloon expandable. Though earlier used, it was later detected that BMSs caused inflammation, platelet activation, thrombosis, and proliferation of vascular smooth muscle cells (VSMCs). Newer stents having significantly thinner struts were made with cobalt-chromium alloys without compromising radial strength or corrosion resistance [10]. Even though this reduced the rate of restenosis compared with balloon angioplasty, in-stent restenosis (ISR) continued to develop in 20%–30% of lesions [10-13]. Due to exuberant neo-intimal accumulation, scar formation occurs with ISR even though stents prevent arterial recoil and stabilize vascular dissections. BMS when coated with materials such as gold, carbon in the form of diamond, phosphorylcholine (PC), which can mimic the cell membrane, and heparin (to prevent thrombosis) did not offer any benefit [14]. Different hormonal receptors such as estrogen, glucocorticoids, and mineralocorticoids when activated or antagonized had modest effects about preventing thrombosis [14-16]. On the other hand, when BMS was coated with anti-proliferative drugs such as sirolimus or paclitaxel it substantially decreased ISR when compared to the non-coated BMS [17-19]. Coroflex® (B-Braun), Driver® (Medtronic), and Vision® (Abbott Vascular), which are made up of cobalt-chromium are some of the widely used BMSs [20]. The recent development in the field of BMS is the use of the element platform, such as in

Omega® stent (Boston Scientific), a platinum–chromium alloy that allows modified architecture, radial strength, thin struts, high radiopacity, and conformability. These stents are cost-effective and had low ISR risk in the selected patient groups [21].

3.2 Drug-eluting stents (DES)

The development of DESs marked a milestone in the treatment of CAD. Compounds that target to reduce inflammation, platelet activation, thrombosis, and VSMC proliferation were tested for DESs. Sirolimus, an immunosuppressive drug derived from a fungus inhibits the mammalian receptor target of rapamycin (mTOR), which in turn causes cessation of cell-cycle progression from the late G1 to S phase leading to inhibition of VSMC proliferation [22]. Paclitaxel is an anti-cancer drug obtained from *Taxus brevifolia*, which acts by disturbing cellular microtubule organization that causes inhibition of cell proliferation and migration [23]. These drugs are coated as a polymeric film on the BMS surface allowing the controlled drug release. The sirolimus-eluting stent was first implanted in 1999 and was later made clinically available as CYPHER® (Cordis) stent in 2002. CYPHER® was tested in many randomized controlled trials (RCTs), including RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, and ISAR-DESIRE. Results of these trials indicated a decrease in ISR and target vessel revascularization compared to the usage of regular BMS [17, 18, 24]. TAXUS® (Boston Scientific), a paclitaxel-eluting stent (PES) is similar to CYPHER® and many RCTs (TAXUS 1–IV) were carried out to confirm its efficacy versus normal BMS [19, 25].

3.3. Biodegradable stents (BDS)

BMS and DESs were superseded by biodegradable stents (BDSs) due to increased incidence of chronic inflammation, angiogenesis [26, 27], restenosis, obstruction of side branches, and late stent thrombosis (LST) via stent fracture [28]. Biodegradable polymers when used for stent coating were thought to possibly mitigate the late stent/polymer vessel interactions [26]. BDSs are made of biodegradable polymer that offers maximum drug loading capacity. When the polymer ratio or composition is varied on the abluminal and luminal sides, it facilitates a better-targeted drug delivery limiting smooth muscle cell proliferation on the abluminal side, while simultaneously encouraging endothelialization on the luminal side [29, 30]. BDSs further facilitate repeated per-cutaneous revascularization or surgical intervention [31]. Moreover, being biocompatible, the BDSs offer another advantage over BMSs and DESs by providing better diagnostic interpretation with magnetic resonance imaging (MRI)/computerized tomography (CT) due to the absence of blooming factor from metallic artifacts [32]. Additionally, BDSs may mitigate the patient's concerns about permanent implants mainly in the current climate of late stent thrombosis. As BDS disappears with time, it helps to reduce the long-term risks associated with a stent such as thrombosis, thus narrowing the need for dual antiplatelet therapy [33]. Owing to the varied degradation time of polymeric stents, ranging from 6–24 months, polymeric stents can also be used both for scaffolding and as a carrier/vehicle for drug delivery, as they are more flexible than metals. Polymeric materials, such as poly-L-lactic acid (PLLA), polyglycolic acid (PGA), poly(D, L-lactide/glycolide) copolymer (PDLA) and polycaprolactone (PCL) have been widely studied for this purpose [34, 35]. The preclinical analysis of histopathological conditions of biodegradable polymer of porcine (PLA [polylactic acid] and PGA) sirolimus-eluting stents (SES) showed lesser incidents of cellular inflammatory response and neointimal formation compared to the permanent polymer SES and BMS on 28, 90, and 180 days post-implantation [36]. Similar results were also noted in the NoboriTM biolimus-eluting stent (Terumo, Tokyo, Japan) when compared with a permanent polymer SES [37], and the stainless steel

sirolimus releasing combo stent (OrbusNeich, Wanchai, Hong Kong) with a biodegradable SimBioSYS coating and anti-CD34 antibody coating in a porcine model [38]. Trials conducted by LEADERS proved that biodegradable polymer-based biolimus eluting stent (BioMatrix FlexTM, Biosensors, Biosensors International, Tokyo, Japan) was non-inferior to that of permanent polymer SES for a period of one year. COMPARE II and NOBORI trials evaluated a biolimus-eluting degradable PLA polymer stent (Nobori, Terumo; 6–9 months degradation time) showcasing clinical non-inferiority versus EES at one year [36]. Other iterations of biodegradable polymer-coated stents such as the Excel stent (JW Medical Systems, Shandong, China [40], sirolimus-eluting bioelute stent with a PLA or PLGA [poly(lactic-co-glycolic acid)] polymer Orsiro stent (Biotronik, Berlin, Germany [41]) and the Coracto stent (Alvimedica, Istanbul, Turkey [42]) are currently being evaluated in clinical trials. Polymeric biodegradable stents have shown several limitations as they are not as strong as metallic stents, which can cause early recoil after implantation. A significant degree of local inflammation also limits its use. Furthermore, the bio-absorption rate is also relatively slow and may still cause restenosis. Moreover, polymeric biodegradable stents are radiolucent, impairing accurate positioning and making it difficult to deploy the stent smoothly and precisely without fluoroscopic visualization. The polymer used may also have a limited mechanical performance of nearly 20%, which requires the use of thick struts that obstructs their profile and delivery capabilities especially when stents are used in small vessels [26].

3.4 Bioabsorbable stents

Metal bioabsorbable stents are an extremely attractive approach that offers comparable performance to that of stainless-steel metal stents. Moreover, they also do not suffer from the limitations like polymeric-based stents. They are classified into two classes namely Mg-based [29, 43-45], and Fe-based alloys [46-48]. These metals are known to have better mechanical properties over other polymers used for duplicating the properties of 316L Stainless steel. 316L stainless steel is the most widely used alloy for fabricating stents and is also often considered a standard reference for mechanical properties when developing new biomaterials for stent applications [49]. Thus, a bioabsorbable stent with metal components has additional benefits when compared to its counterpart polymeric stents. The first-ever patented 'metallic stent, which is degradable *in-vivo*,' was issued in 2002 [50]. The most recent patented stent has a base body whose core is made up of bio-corrodible alloy selected from the group consisting of magnesium (Mg), iron (Fe), zinc (Zn), and molybdenum (Mo), along with a diffusion layer containing arsenic (As) and selenium (Se) which covers the core [51]. Among all, Fe and Mg are the first choices due to their known effect on human metabolism [43, 46]. Fe and Mg are well recognized to possess low toxicity and well-established clearance mechanism [52]. The cytotoxic side effects of Fe were also insignificant as the degradation rate is extremely slow under *in-vivo* conditions when compared to its benefits [46]. Due to the slower degradation rate and a small amount of Fe in a coronary stent (stent weight~40 mg) when compared with the high Fe-load of blood (447 mg L-1) shows relatively unlikely systemic toxicity [53]. The toxicity of Mg is also insignificant as the amount of Mg in blood plasma is tolerable up to a relatively high level of 85-121 mg/L, [54], and is countered due to efficient excretion of Mg in the urine [55]. Fe stents have better mechanical properties when compared to Mg alloys. Stents having SS316L also have similar properties as that of the Fe stents. Metals such as calcium (Ca), manganese (Mn), Zn, and rare earth metals are also tolerated in the human body and can also be used

for stents [56]. Unlike most metallic biomaterials, Fe is ferromagnetic which may interfere with MRI observation due to its ferromagnetic properties. However, the ferromagnetism of Fe can be altered when combined with Mn, which leads to anti-ferromagnetism and improved mechanical properties [29, 47].

3.5 Endothelial progenitor cell (EPC) technology stents

Though DESs can effectively reduce restenosis after a PCI, they can also delay the re-endothelialization time and impair microvascular function, eventually leading to undesirable clinical outcomes. The endothelial progenitor cell (EPC) offers a functional layer of endothelial cells on the stent surface which causes improvement in microvascular function [57]. Circulating EPCs are capable of reaching the site of vasculature and contributing to re-endothelialization and inhibiting the development of neointimal hyperplasia. Anti-human CD34 antibodies when incorporated onto the stent surface facilitate colonization of circulating EPCs onto the stent struts which accelerates the re-endothelialization of the stented artery segment. The EPC capture stent is covalently coupled with intermediate polysaccharide coating and with murine monoclonal anti-human CD34 antibodies which are attached to a stainless-steel stent with the help of a dual helix design (R stent, OrbusNeich, Fort Lauderdale, FL, USA). These antibodies specifically target CD34-positive cells, including but not exclusive to EPCs found in the circulation. It is contemplated that the captured EPCs can mature into functional endothelial cells and covers the luminal stent struts. Pro-healing stents result in lower incidences of restenosis and thrombosis, thus obviating the necessity for prolonged dual antiplatelet therapy. TRIAS program-initiated TRI-stent Adjudication Study (TRIAS), a prospective, single-center, randomized, pilot-scale study comparing the treatment with EPC capture stent and paclitaxel-eluting stent showed an insignificant difference in target vessel failure (20.4% vs. 15.8%). Despite being less effective than the paclitaxel-eluting stent, it has encouraging results regarding the "no stent thrombosis'' observation in the EPC capture stent group when compared to 5 cases (in 4 patients) of stent thrombosis in the paclitaxel-eluting stent group [58, 59]. GENIUS-STEMI Trial, a randomized comparison of Genous Stent versus Chromium–Cobalt Stent for Treatment of ST-Elevation Myocardial Infarction (GENIUS-STEMI) was conducted as a single-center trial to compare the outcomes of patients in the group of an EPC capture stent or a cobalt-chromium BMS. After a 6-month follow-up, the rate of major adverse cardiac events and target lesion revascularization in the EPC capture stent group on being compared with the cobalt-chromium BMS group, was 24% versus 10% respectively, indicating the latter to be better. In addition to the excellent safety data showcased in the above-mentioned studies, there were 3 cases (6%) of stent thrombosis in the EPC capture stent group versus none in the cobalt-chromium BMS group [60]. A sirolimus-eluting bioengineered stent called the "Combo stent" (OrbusNeich Medical, Fort Lauderdale, FL, USA) was designed, which was a combination of EPC capturing technology with abluminal elution of sirolimus to control neointimal proliferation. The drug/polymer coating contains sirolimus loaded in the biodegradable SynBiosys™ polymer Octoplus. The total drug content is estimated to be half the dose of the commercially available sirolimus-eluting stent having the same release profile. The polymer degradation occurred between 90-180 days. The Combo stent was evaluated in the REMEDEE study, a prospective, multicentre, randomized clinical trial evaluating the abluminal sirolimus-coated bio-engineered stent (NCT00967902). In this study, the Combo stent was compared with a commercially available paclitaxel-eluting stent in 183 patients. Results showed 8.7%

rate of major adverse cardiac events in the Combo stent group after 9 months as compared to 11.0% in the paclitaxel group. Both groups reported 0% stent thrombosis after following up for 9 months [58].

4. Complications associated with stenting

Several reports indicate evidence of local arterial reactions due to balloon dilation or stenting, followed by a series of inflammatory events in response to injury. Data obtained from human studies have shown an acute inflammatory cell response within 0 to 3 days in the area of stent struts. Damage is associated with the trauma experienced by the surrounding cells. The stimuli for the inflammatory response are attributed to the disruption of the coronary endothelial layer, which activates and aggravates the release of inflammatory cells, ultimately leading to neutrophil deposition and macrophage accumulation at the tissue injury site [61, 62]. Acute inflammation reduces after 2–4 weeks, followed by the progression of chronic inflammation and proliferation of smooth muscle cells, leading to thrombus formation along with the thinning of extracellular matrix. With the passage of time only fibrin and chronic inflammation persist. The smooth cells' extracellular matrix (proteoglycans and collagen) is necessary for the enrichment of expanding neo-intima [63]. Although coronary stents offer some advantages over balloon angioplasty, their use is reported to cause more fatal arterial damage and inflammatory response within the vessel walls [64]. The presence of an intravascular residual metallic foreign material causes an ischemic phenomenon due to endothelial dysfunction. The stent struts cause focal deep vascular trauma and worsening of the initial inflammatory reaction (Figure 1) [65]. Moreover, main inflammatory and proliferative reactions are not limited to the vessel wall but extend from the injured vessel throughout the surrounding tissues, including the neighbouring myocardium [66, 67].

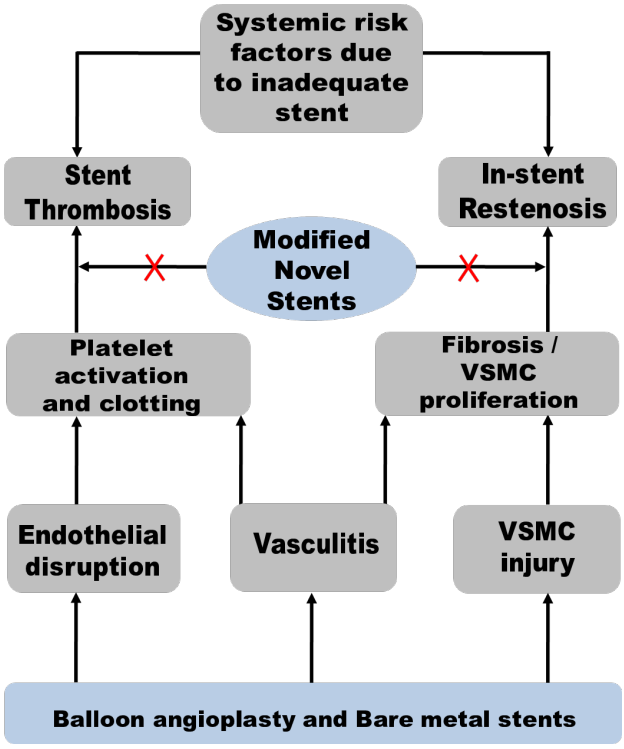

Figure 1: Schematic representation of destructive events arising after implantation of coronary stents.

4.1. Inherent Thrombogenicity

Stents are recognized as foreign bodies in the vessel wall which induce processes, such as platelet adhesion activates coagulation factors leading to inevitable thrombosis. Platelet activation should be inhibited following the stent delivery. Currently, low rates of early stent thrombosis (1%–2%) [68, 69] can be addressed by tolerance and adherence to dual anti-platelet therapy with aspirin and thienopyridine. However, it is not advisable to recommend this therapy to patients who have an increased risk of bleeding incidents or those requiring surgeries [70]. Furthermore, there is an increased risk of significant morbidity, including gastrointestinal bleeding, anti-platelet hypo-responsiveness, and the subsequent greater risk of stent thrombosis [81, 82]. To mitigate the incidence of late thrombotic events, it has been advised to

follow dual anti-platelet therapy after DES placement although, no conclusion has been drawn in favour of the extended regimen [73, 74].

4.2. Delayed re-endothelialization

The speed of re-endothelialization can be a major indicator of the success in the clinical trial outcome of stents. Endothelial cells migrate from intact neighbouring coronary segments or from circulating EPCs toward the vascular injury site [75] to re-endothelialize the injured artery. It is shown that both Sirolimus and paclitaxel are known to actively suppress endothelial cell growth *in-vitro* [76-78] and impede EPC homing and proliferation *in-vivo* [79-81], thus delaying the re-endothelialization.

4.3. Metal and Polymer Coating Hypersensitivity

Metal alloys such as nickel and molybdenum caused hypersensitivity in ~10% of patients with BMS implantation [82]. Few events of inflammatory responses were reported when stainless steel was used [82, 83]. The severity of inflammation directly relates to the extent of restenosis. Significant hypersensitivity reactions have also been noticed with the polymer-coated DESs. Post DES implantation, eosinophilic infiltrations in adventitia with spontaneous coronary dissection can act as major hallmarks of inflammatory response in patients [84]. Severe DES-related clinical complications exhibit necrotic core prolapse in-stent restenosis and LST preventing arterial healing [85].

4.4. Poor Coating Integrity

Another important factor that is often neglected in the stent safety profile is the coating integrity after crimping and expansion. Some studies have reported the widespread possibility of coating delamination in commercially available DESs [86-88], however, it is still considered to be safe by the Food and Drug Administration (FDA) [88]. In addition to this, DES polymer coatings have other risk factors, such as surface cracking, peeling, and flaking at the polymer-metal interface [89-91]; exposing the underlying thrombogenic metallic substrate and thus contributing to the chronic inflammatory and hypersensitivity reactions [92, 93].

5. Characterization of stents

To overcome the above-mentioned incompatibility reactions *in-vitro* and *in-vivo*, biocompatibility tests must be performed, which are broadly classified as physical and mechanical characterization.

5.1. Physical characterization

Critical rigorous testing is important for the safety and efficacy of stents. As per FDA recommendations, the stent should be able to withstand nearly 10-15 years of pulsating load under *in-vivo* conditions or within the human body. The stent should be able to withstand exhaustive loading and unloading of 600 million cycles/heat pulses. Therefore, it is vital to perform rigorous pulsatile fatigue tests and mechanical tests for the entire lifecycle of the product. Other aspects, such as raw material characterization, stent design selection, component testing, and stent characteristics should also be taken into account for validation of safety and effectiveness [94].

The methodology obtained has two parts namely: a). A mechanical analysis to calculate the stability of stent under cyclic loading and shakedown state [95]. b). Fatigue analysis to determine the number of cycles with appropriate fatigue criteria based on the previous stabilized cycle [95].

5.1.1 Mechanical analysis of stents

5.1.1.1. Raw Material Testing

Metals including L605 cobalt-chromium, 316L stainless steels, or Nitinol-based shape memory are commonly used alloys as they meet the required mechanical properties for service and deployment

and have better corrosion resistance and increased biocompatibility [95-98]. L605 cobalt-chromium alloys are known to have higher fatigue strength than stainless steel. Fracture mechanisms and fatigue properties of Nitinol are still not completely understood. Microstructure can be used to determine fatigue behavior and the cyclic hysteresis response of the metal alloy. Fine-grained materials and coarse-grained materials are known to have resistance to fatigue crack initiation and fatigue crack growth, respectively. Fatigue crack initiation is of significant relevance for stents and hence fine-grained material is preferred. The usual thermo-mechanical processes can reduce the size of the grain to about 10 nm for 316L stainless steel and cobalt-chromium alloys or 100nm for nitinol alloys [95-98]. Nitinol possesses unique properties such as greater elongation ability to recover shape, contract, and relax in varying temperatures, thus the metal is referred to as a "shape memory" alloy, or a "super-elastic" metal [94].

5.1.1.2. Stent design selection

High precision laser cutting is used to create the mesh pattern of a stent which can form simple or complex geometries. Wire braiding, laser tube cutting, or laser sheet cutting are used to form various patterns. The most common pattern is the diamond structure. Fatigue mechanical testing is done on diamond structure subsets for optimizing the stent body geometry. These tests provide data regarding different diamond structures. They are carried out in positional control at 60Hz to determine and compare the performance of one geometry with another geometrical configuration during fatigue testing [94].

5.1.1.3. Stent deployment testing

A stent is used in the angioplasty of a coronary artery to clear the build-up of plaque or a blood clot, which causes narrowing/blockage of the blood vessels. A needle is inserted into the femoral artery and the guide wire is passed through the inserted needle to guide it to the artery to reach the clot or blockage. A catheter is slipped up to the heart before reaching the site of clot or blockage. Once the catheter is placed in its appropriate place, the guide wire is removed followed by the insertion of the second guide wire with a collapsed stent. Many stents have balloons incorporated into them which can inflate the collapsed stent. The pathway of this process can encounter many frictional properties; therefore, it has to be quantified appropriately so that the patient is not harmed. Tests such as tortuosity and universal testing systems are often used to measure these frictional properties. Lubricants and surface coatings can be used to either increase or decrease the guide wire and catheter frictional properties [94].

5.1.2 Fatigue testing of stents

Fatigue testing combined with computational analysis may act as a prominent indicator of the stent's durability. It can be used for identifying conditions that are not modeled using computational methods and also for validation of fatigue analysis [95, 99]. Accelerated durability testing of stents is conducted inside synthetic arteries with a stent deployed. The artificial arteries are designed in such a way that they can simulate pulsatile loading, body temperature, and salinity. The physiological environment is maintained with phosphate-buffered saline, Ringer's, or Hank's solution maintained at 37º C. The loading frequency can range from 20 to 100 Hz (the normal heart rate is approximately 1.2 Hz). Other types of cyclic loading (e.g., bending, compression) or different configurations of stents (e.g., overlapping), or synthetic arteries (e.g., bent to a curvature radius) can also be considered. Recent studies on explanted stents from human autopsy retrievals have revealed *in-vivo* corrosion of stents with a significant release of metallic ions into surrounding

tissues. Tests including mechanisms of pitting, fretting, crevice, and galvanic corrosion are recommended [95, 99, 100]. Arterial curvature, a biomedical factor combined with stent overlapping can increase the incidence of wear and fatigue fracture, which contributes to micro motions between the overlapping portions [95, 101, 102]. Performing stress or strain-based tests is usually based on understanding the *in-vivo* cyclic conditions and the material type [95, 98] (Figure 2). Limitations include the effects of size, experimental specimens, and dimensions; not every manufacturing process is reproducible, and complex *in-vivo* loading conditions are not easy to simulate [96].

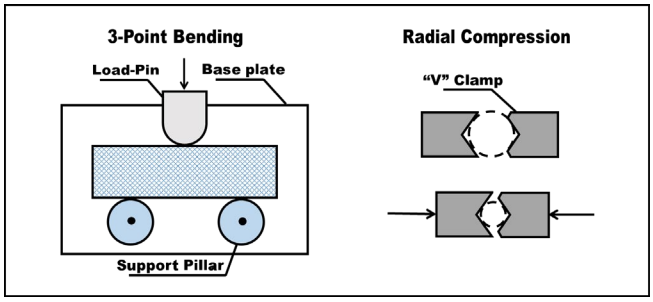

Figure 2: a) Schematic Representation of Three Point Bend test. b) Schematic representation of radial uniform compression test [98].

5.2. *In-vitro* Characterisation

5.2.1 Drug-eluting stents

5.2.1.1 In-vitro dissolution testing: This flow-through cell system is designed to analyze drug release from DESs and is approved by the FDA [103-106]. A closed system setup consisting of low media volumes is used in two types; the compendial tablet cell and the non-compendial implant cell. The flow of media through the cell is similar to that of the flow-through arteries. The flow rate can be adjusted as per requirements to mimic the blood flow velocity in the coronaries [106]. The stent position should also be considered when the compendial flow-through cell is used [107,108]. The reciprocating holder is made up of a media-filled container and an immersed holder can be used to attach the dosage form. The vertical reciprocation of the dosage form is performed at a frequency of 30 dips/min. The mechanical stress which acts on the dosage form can be adjusted by varying the dipping rate. A non-compendial stent holder helps in avoiding contact with the side of the tubes. The stents are placed in vials or flasks of small volumes containing the dissolution media [108-110]. Samples are withdrawn at predetermined time points and are replenished with fresh media. The challenge associated with this is its bio-relevance as the body lacks the sink condition, which is maintained during the experiment [111]. The flow-through cell flow chosen should be able to emulate the *in-vivo* situations. A hydrogel compartment in the cell can act as an alternative acceptor compartment apart from the dissolution media. The shape of the hydrogel represents the human lumen where the media can be circulated. The balloon catheter can be used to place the stent inside the lumen [112] (Figure 3).

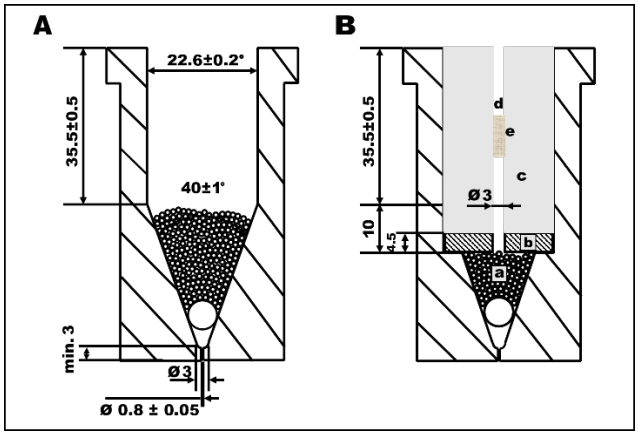

Figure 3: Pictorial Representation of vessel simulating flow-through cell. a) Glass beads. b) Hydrogel. c) Acrylic glass disc. d) Aperture for media flow. e) Stent [112]

5.2.1.2 Accelerated Release Testing: This test is more about quality control rather than a real-time study.

But otherwise, it should also be able to predict real-time dissolution [113]. Methods that employ changes in the composition of the dissolution media (ionic strength, pH, the addition of co-solvents, enzymes, or surfactants), rise in temperature, or increase in mechanical stress (e.g., agitation or flow rate) can be used to study the accelerated release from the polymers [114-117]. It accelerates both the drug release as well as the underlying mechanism of the same [118]. Merciadez et al. studied accelerated dissolution tests on Cypher stent [103]. Flow-through cell with sodium dodecyl sulfate and acetonitrile as release media was used. The dissolution study was carried out for 24 hours which matched the 30-day release in a porcine model. The total porosity of the polymer matrix was increased due to the addition of acetonitrile in release media during a study carried out by Kamberi *et al.*, leading to accelerated release [114].

5.2.2 Biodegradable stents

In-vitro methods such as electrochemical tests, a hydrogen evaluation tests, and weight loss tests can be used to mimic *in-vivo* degradable processes [119-121]. Different *in-vitro* simulating systems have been established by researchers that use different electrolyte solutions and varied ratios of sample-to-solution volume to help in producing comparable data. Hence, except for subjective factors such as the element of choice, coating on the surface, and processing technology, the principal objective must be as close as possible to *in-vivo* conditions. Other factors such as electrolyte solution selection, surface roughness influence, various test methods (electrochemical test and immersion test), and evaluation methodology of corrosion rate play a vital role.

5.2.2.1 Electrolyte solution: The selection of an appropriate electrolyte solution that mimics body fluid is one of the most important factors in obtaining good and reliable data. Mostly simulated body fluid (SBF); 0.9% NaCl aqueous solution, DMEM, Hank's, or phosphate-buffered saline is used [119].

5.2.2.2 Surface roughness: Different surface treatments are used to improve the corrosion properties of the biomaterials. Treatments such as coating or oxidation, and blast sanding are intentional changes, but surface roughness on corrosion properties is ignored to a large extent [119].

5.2.2.3. Electrochemical test: This is an easy and convenient way to determine the corrosion property by either testing the polarization curves and electrochemical impedance spectroscopy (EIS), or open circuit potential (OCP) using a three-electrode system [119].

5.2.2.4. Immersion test: Biodegradable metallic materials are evaluated for corrosion properties by this method as per ISO 10993-15 [121] and ASTM G31-72 [122] the materials will be degraded in the solution and the corrosion products are analyzed. As per ISO 10993-15, these tests should be carried out in a tightly enclosed container to prevent evaporation. The temperature should be maintained at 37°C for 7 days and factors such as flow rate, the ratio of solution volume to sample surface area (v/s), the evaluation method of corrosion rate, and the immersion time should be maintained [119]. Four different methods can be used to determine the rate of corrosion of metallic materials. They can be used based on the principle of corrosion and feasibility and are described as:

(A) Mass loss/gain-It evaluates the corrosion rate by using the change in mass of the samples before and after the immersion test. The sample is immersed in a solution (corrosion medium) for a defined period followed by its removal. Thereafter, mass is measured [119].

(B) Hydrogen evolution- It evaluates the corrosion properties of metals such as Mg alloys that can produce gas when immersed in a simulated body fluid. The volume of hydrogen can be used to determine the corrosion rate [119].

(C) Released ion concentration-Corrosion rate of metallic materials is calculated by using the released ion concentration in the immersed solution. The immersed solution has an acid that is inductively coupled with a plasma-atomic emission spectrometer [119].

(D) Electrochemical corrosion current- This is an *in-vitro* gravimetric and electrochemical method to determine the rate of corrosion. It is a non-destructive synchrotron-based microtomographic technique used to test general corrosion rates by observing the time-dependent change in the metallic volume of the remaining implant [119, 123].

5.3. *Ex-vivo* studies

A preliminary study to assess the system's ability to investigate coronary arterial implant thrombosis was performed on polished, stainless steel 7-9 NIR® stents. These trials indicated the system's utility in assessing occlusion time as a rough measure of thrombotic potential. It was measured with various flow profiles such as impulse, square, triangular, sinusoidal, and coronary in a fluid loop run under the nominal geometric and fluidic conditions found in an adult left anterior descending coronary branch [124].

5.4. *In-vivo* studies

Degradable and permanent stents were implanted in the coronary arteries of experimental animals such as Yorkshire pigs [125,126]. The pre-treated and sedated animals received an intravenous access line and were anesthetized with isoflurane after intubation. After the surgical placement of an introducer sheet in the right carotid artery (RCA), the stents were randomly implanted under angiographic control into the RCA, left anterior descendent (LAD), and the left circumflex (LCX) coronary arteries by dual balloon inflation [127, 128]. The embedded tissue blocks were further cut into 5 mm slices for histological, morphometric, and immunohistological assessment [129].

6. Modifications in the existing stents

An enhanced inertness of the metallic implants and therefore reduced rate of thrombogenicity was achieved by using various coating materials such as gold [130], diamond-like carbon [131], pyrolytic carbon [132], and phosphorylcholine (PC) [133], however, it failed to reduce the rate of restenosis. Stents coated with PC were found to be non-thrombogenic both under *in-vitro* and *in-vitro* conditions with no sign of endothelialization and no effect on the rate of stent thrombosis [68, 134]. Stent biocompatibility is actively influenced by host response due to varied physiological conditions, whereas only vascular biocompatibility in the form of thrombogenicity is tested alone at the expense of other aspects. One such example is a heparin-coated stent where design helps to reduce thrombosis but not neo-intimal hyperplasia [68, 135]. A few methods/modifications to develop biocompatible stents can emerge as a potential approach [68, 136-140].

6.1. Nanotechnology for controlled release of drugs and novel stent design for myocardial reperfusion

Polymeric nanoparticles with pharmaceutical agents encapsulated are a novel drug delivery system and can easily hit the target of interest [140-143]. For example, d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) acts as an emulsifier in poly(DL-lactide-co-glycolide) (PLGA)- a biomaterial matrix. These nanoparticles can control the release of paclitaxel and have high encapsulation efficiency for treating restenosis. The high encapsulation efficiency

helps in improving cellular uptake and keeps a check on the cytotoxicity against SMC proliferation [140]. Nevo-sirolimus, a PLGA-based eluting stent, which has an L605 cobalt-chromium alloy has a multi-channel reservoir apart from stent struts and a drug-polymer (sirolimus/PLGA) matrix for elution [144], which was found superior to the traditional paclitaxel-eluting stents (TAXUS Liberté) in clinical trials [145]. Patients undergoing PCI and with acute ST-segment elevation myocardial infarction (STEMI) have sub-optimal optimal myocardial reperfusion in general. Thus, the design should be able to prevent thrombus protrusion into the lumen after PCI in case of acute myocardial infarction. Polyethylene terephthalate (PET) micronet mesh thin strut metal stent (MGaurd) was evaluated for its functional design to trap and exclude thrombus and atheromatous debris which prevents distal embolization [68, 146]. The stents showcased better rates of epicardial coronary flow and complete ST-segment resolution when compared to conventional metal stents. Larger clinical trials can provide better clinical outcomes [146].

6.2. Plasma Polymerization

Plasma was discovered as the fourth state of matter which can be artificially generated when dielectric gas is subjected to ionization by free electrons which are accelerated under a high strong electric field [147, 148], modifying their surface energy, chemistry, and charge without changing bulk properties [149]. Argon is reacted with acetylene in the plasma deposition system, and a plasma-activated coating (PAC) is created on the metallic biomaterial surface which is recommended in stent application. The carbon polymeric layer is the reservoir for free radicals which helps in effective and covalent protein attachment [150, 151]. Pulse-biased plasma polymerization is used for metallic substrates having covalent biomolecules for immobilization, which thereby reduces the complex chemical linker-based bio-functionalized process [152]. Direct covalent attachment with horseradish peroxidase, tropoelastin, and catalase was exhibited between protein binding and biomolecule activity on PAC with stainless steel [150, 153]. PAC on a 316L SS stent binds covalently on a dense layer of recombinant tropoelastin, which facilitates the growth of endothelial cells [154]. Plasma-modified stents having tropoelastin surfaces have better blood biocompatibility, improved endothelization, and reduced clot formation. Preclinical studies on PAXC showed better feasibility and delivery with greater potential as a local biomolecule carrier [155].

7. Future prospects

Stent technology has undergone revolutionary advancements in design and mechanism of action over several decades of its existence, enabling a drastic reduction in the rates of in-stent thrombosis and restenosis. Improved design of BMS and DES, use of biodegradable polymer coating, and use of antiplatelet therapy and high-pressure inflation are some of the major advances that have resulted in this drastic reduction. However, the technology still has a scope for improvement to achieve better efficacy and reduce in-stent thrombosis and restenosis, and other associated complications further. With the advent of nanotechnology, new coating materials such as nanotextured surfaces, nanothin coatings, and nanoparticulate coatings are being tested for improved biocompatibility [156], Use of ultrathin struts and bioresorbable polymers in clinical trials have demonstrated improved safety and efficacy [157]. Additionally, newer therapeutic agents that selectively target vascular smooth muscles and fast polymer-free drug-eluting stents are also being tested [158]. With these newer advances, it is hoped that in the near future stent implantation will result in close to zero percent adverse events.

Conclusion

The rate of ISR in CAD patients is on the rise causing widespread health implications. This has led to tremendous development in the field of coronary stent development with an interest in DES. Newer approaches are focused on reducing the inherent thrombogenicity, delayed re-endothelization, metal and polymer coating hypersensitivity, and poor coasting integrity arising because of stent incompatibility after implantation. For improving the overall stent property, sophisticated strategies are currently being used for the characterization of stent properties as most of the bio-incompatibility issues are associated with the adverse issues of biomaterials. Material characterization for achieving the highest biocompatibility could be achieved by doing physical, ex-vivo and *in-vivo* characterizations. Though most of the recent advancements in stent development have addressed the demanding needs of CAD patients, however, these strategies still require modifications to meet the patient needs and care.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

S.R.B and V.K performed the literature search and wrote the first draft. J.K and S.G revised the 1st draft. A.D and A.B conceptualized, revised, and reviewed the manuscript. All authors have approved the final version of the manuscript.

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