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Review

The Development of Coronary Artery Stents: From Bare-Metal to Bio-Resorbable Types

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Abstract: Coronary artery disease is the leading cause of death worldwide. Conventional balloon angioplasty is associated with high rates of complications such as coronary dissection and vessel recoil. The deployment of bare-metal stents (BMSs) can overcome these problems and achieve a better patency rate than simple balloon angioplasty. It has been shown that the stent design including structure platform, size, length, and strut thickness has a major influence on the clinical results. Even though angioplasty with BMS implantation is widely used in coronary interventions, the restenosis rate due to neointimal hyperplasia remains high. Therefore, drug-eluting stents (DESs) coated with anti-proliferative agents and polymers have been developed to reduce the restenosis rate and improve the clinical outcomes. Although the repeat revascularization rate of DESs is lower than that of BMSs, the long-term stent thrombosis rate is higher than for BMSs. Therefore, new and emerging generations of stents, in which, for example, thinner struts and bioresorbable polymers are used, are available for clinical use. However, there are only a limited number of clinical trials, in which these newer stents have been compared with BMSs and first- and second-generation DESs. The purpose of this review was to provide up-to-date information on the evolution of coronary artery stents from BMSs to DESs to bioresorbable stents (BRSs).

Keywords: coronary artery disease; stent; bioresorbable; drug; polymer; strut

1. The Evolution of Coronary Stent Development

Coronary artery disease (CAD) is a major cause of mortality and morbidity. One of the treatment options for CAD is a percutaneous coronary intervention. Balloon angioplasty alone, which involves pushing the plaque to the walls of the artery, can achieve a larger luminal diameter in the acute phase. However, arterial recoil, dissection, and late neointimal hyperplasia can result in vessel restenosis. Therefore, bare metal stents (BMSs) made from metallic materials were developed to overcome the dissection and the restenosis complications caused by recoil. Although the restenosis rate can be reduced by stenting, the in-stent restenosis (ISR) rate is still high at around 20%–30% [1,2]. ISR is mostly caused by neointimal hyperplasia.

A reduction in restenosis was first achieved with the evolution of the stent platform, including thinner stent struts and new metal compounds. Furthermore, new drug delivery systems and polymer coatings have been developed to achieve better clinical outcomes. The first generation of drug-eluting stents (DESs) with a sirolimus or paclitaxel coating showed better clinical outcomes with lower rates of cardiac death, myocardial infarction, and target vessel revascularization than BMSs [3,4]. However, increased rates of stent thrombosis were reported with first-generation

DESs, and second-generation DESs with thinner struts, different anti-proliferative drugs and polymers were subsequently developed to reduce the rate of long-term cardiac adverse events. More recently, bioresorbable material has been developed for use in stents. Even though the long-term outcomes are unknown, this material and new designs have changed the application of percutaneous coronary intervention.

In the present work, we review the evolution of coronary stents, from BMSs, through first-generation DESs, to today's fully BRSs. Aspects covered in this review are materials, design, and clinical performance.

2. Stent Structure

A coronary stent is designed to maintain vessel patency. An ideal stent should have good biocompatibility, flexibility and deliverability, low thrombogenesis, strong radial force to maintain a large vessel diameter, good radio-opacity under fluoroscopy, and low rates of neointimal hyperplasia and stent thrombosis during long-term follow-up.

A classic stent is composed of three components: a metallic platform, polymer coating, and anti-proliferative drug. BMSs are constructed from metallic alloys without drug elution, including many different platforms such as stainless steel, platinum-chrome, tantalum, and cobalt-chrome. Stainless steel (316 L) is a mixture of 95% iron and 5% nickel, and is poorly visible under fluoroscopy. Tantalum alloys have poor radial force and easily recoil. Cobalt-chrome alloys have better radial strength and radio-opacity, and most stents are currently made from chrome with cobalt or platinum struts. Platinum-chrome alloys are twice as dense as cobalt-chrome alloys, and so have better radio-opacity under fluoroscopy. Alloys other than those containing stainless steel can allow for thinner struts while maintaining radial force. The first-generation DESs had thick struts of around 130–140 μm, while the next generation had thinner struts of around 70–90 μm, resulting in a decrease in both the rates of angiographic and clinical restenosis [5]. The coating of the metallic surface, including chromium oxide or gold, can reduce biological interactions with blood, however, a gold surface has been shown to result in a high incidence of restenosis. Except for balloon-expandable stents, most self-expandable stents are made from nitinol, which can maintain its initial shape within the vessel.

Even with the same material, different configurations can be used to create different designs. Stent designs include wire coils, slotted tubes, and a modular design. Wire coils are formed using 0.15 mm circular metallic wire to create loops and folds for expansion. However, few connections between struts results in good flexibility but poor radial force, and coil-type stents are thus no longer available. Slotted tubular stents were designed to replace wire coils stents to increase radial strength, and they include some articulation between the stent segments. The drawback of this design is poor flexibility due to the rigid structure, although recent improvements in design using laser cutting have resulted in improved flexibility without compromising strength. Another issue in stent design is the use of closed or open cells in multicellular stents. An open cell design allows for better flexibility and deliverability, side branch access and tolerability on bending. In comparison, a closed cell design can provide better vessel coverage and radial strength but less flexibility. Modular stents can overcome the problems with flexibility in slotted tube stents. They are comprised of multiple repeat modules joined together to construct a stent tube, which can provide good flexibility and side branch access.

The cross-sectional shape of a stent is another factor in its design. Some stents have round struts with no edge or square struts. Round struts can reduce turbulent blood flow and avoid cells' disruption. In addition, different sizes and lengths of the stent can also affect the clinical outcomes. A large diameter involves a large vessel area and less late loss, whereas a longer length of stent increases the rate of restenosis in BMSs but not in DESs [6]. The stent coatings are designed to reduce thrombotic events and restenosis, and include heparin-based, phosphorylcholine (PC), and carbon.

Another important component of a stent is the polymer, which is used as a carrier for anti-proliferative drug release. Polymers have been reported to result in an inflammatory effect leading to thrombosis [7]. To overcome this problem, newer stents are polymer-free or use bioresorbable polymers. As a polymer degrades, endothelial healing improves, and so polymer-free or bioresorbable

stent designs may prevent the early complications of BMSs and improve the later complications of DESs. This will theoretically reduce the rate of stent thrombosis, however the long-term outcomes need to be verified in large randomized controlled trials.

3. Bare Metal Stents

Coronary angiography and balloon angioplasty were introduced in the late 1970s. Initially, plain balloon angioplasty without stent implantation showed high rates of arterial recoil and vessel dissection. The first coronary stent was implanted in 1986. Coronary stents can seal dissected tissue and avoid elastic recoil, and they have been shown to result in better outcomes than plain balloon angioplasty [1,2]. Therefore, coronary stents have become the most common therapeutic intervention for CAD. However, BMSs have a high rate of ISR due to neointimal hyperplasia with smooth muscle migration and proliferation [8]. A previous trial reported an ISR rate of 10%–20% during six months of follow-up which resulted in myocardial infarction and angina requiring revascularization [9].

Initial stents made from stainless steel have thick struts. Because of poor flexibility and high ISR rate, stents with thin struts were developed [5,10]. The stainless steel was replaced by cobalt, chromium, or other elements to maintain the strength and radio-opacity. Cobalt-chromium alloys are used in Multi-Link Vision L605 (Abbot Vascular, CA, USA), Coroflex (B. Braun, Berlin, Germany), and Driver MP35N (Medtronic, Santa Rosa, CA, USA) stents [11,12]. Other compounds, including a platinum-chromium alloy in Omega (Boston Scientific, Natick, MA, USA) stents and a cobalt alloy in Integrity (Medtronic, Santa Rosa, CA, USA) stents were developed. These compounds allow for thinner struts and have better radio-opacity, deliverability, and conformability, however the ISR rate is still high at around 15% after follow-up of 6 months [11,12].

Several inorganic coatings on the stent surface have been developed to minimize metal ion release, including diamond-like carbon, iridium oxide, titanium-nitride-oxide, and silicon carbide. However, clinical trials have not shown any benefits in the ISR rate with these coatings [13–16]. Therefore, the development of a drug-eluting polymer coating has become an important area of research to overcome this problem. Despite the application of new anti-proliferative drug-eluting technology, the stent platform and coating still play an important role in stent design, even though polymer-free stents and those using bioresorbable polymers are used currently.

4. Drug-Eluting Stents

The application of anti-proliferative agents was a major breakthrough in coronary artery stent design. The major goal of a DES is to reduce ISR by inhibiting neointimal hyperplasia. Several factors affect the drug elution from polymers, and how best to release the drug and the duration of drug elution are the most important issues in DES design.

4.1. First-Generation DESs

The structure of the first generation of DESs was based on a stainless steel platform coated with a drug-eluting polymer. Two widely used DESs were the Cypher (Cordis Corporation, CA, USA) and Taxus (Boston Scientific, Natick, MA, USA) stents first introduced in 2003, both of which were made of stainless steel and had a stent strut thickness of about 135 μm. The Cypher stent had a Parylene tie-layer and polyethylene-co-vinyl acetate (PEVA) and poly-*n*-butyl methacrylate (PBMA) polymer with a sirolimus coating. Sirolimus is an immunosuppressant which can inhibit cell proliferation in the G1 to S phase of the cell cycle. The Taxus Express and Taxus Liberte (Boston Scientific, Natick, MA, USA) stents had a poly(styrene-b-isobutylene-b-styrene) (SIBS) polymer with a paclitaxel coating [17]. Paclitaxel is approved for the treatment of ovarian cancer via inhibiting microtubules for mitosis. Both sirolimus and paclitaxel have anti-proliferative effects which can inhibit smooth muscle migration and endothelial healing. The first-generation DESs were reported to have better efficacy with lower rates of ISR and target vessel revascularization than BMSs in a meta-analysis study, with a reduction in the rate of target vessel revascularization by 60%–70% [18]. Other trials have

reported that sirolimus-eluting stents are better than paclitaxel-eluting stents with regards to target lesion revascularization, stent thrombosis and ISR [19–21].

However, after DES implantation, increased rates of myocardial infarction and cardiac death caused by stent thrombosis have been reported during long-term follow-up [22–24]. Stent thrombosis can cause abrupt vessel closure resulting in serious cardiovascular events. The Academic Research Consortium (ARC) reported that the majority of cases of stent thrombosis occur late or very late, with a very late rate of around 0.2%–0.5% per year, which is higher than for BMSs [25]. The high rate of late and very late stent thrombosis is caused by a long duration of drug elution, which can delay endothelial healing and prolong metallic structure exposure to blood vessel [26]. Interestingly, anti-proliferative agents have been reported to reduce the rate of ISR but increase the rate of stent thrombosis. Therefore, how best to balance efficacy and safety is an important issue.

4.2. Second Generation DESs

Second generation DESs were developed to overcome the problem of late and very late stent thrombosis by accelerating vessel healing. These DESs showed improvements in strut thickness, deliverability, and flexibility. The platform was changed to cobalt-chromium or platinum-chromium which allowed for a reduction in the strut thickness. These new stents used more biocompatible polymers such as PC, polylactic acid (PLA), poly(vinylidencefluoride-cohexafluoropropenen) (PVDF-HFP), and polyvinylpyrrolidone (PVP). New coating drugs were also used in second generation DESs, including zotarolimus, everolimus, and novolimus, which were shown to result in good endothelial coverage in an animal study [27].

Zotarolimus is used in the Endeavor and Endeavor Resolute (Medtronic Vascular, CA, USA) stents. The Endeavor stent consists of a cobalt-chromium platform with thinner struts and a PC polymer which has been shown to have better biocompatibility and anti-inflammatory effects, and to provide faster drug elution with earlier vessel healing. Randomized controlled trials have reported that this stent has better results in terms of ISR and repeat revascularization than a BMS [28,29]. The ENDEAVOR III trial reported that a zotarolimus-eluting stent was associated with lower major cardiac events during a five-year follow-up compared to a sirolimus-eluting stent (Cypher, CA, USA), but an increased rate of repeat revascularization was reported in a meta-analysis [29,30]. Moreover, a zotarolimus-eluting stent was associated with a lower rate of cardiac adverse events than a sirolimus-eluting stent in very late stent thrombosis after three years of follow-up [31]. However, Camenzind et al. reported no difference in clinical outcomes at one year between Endeavor and Taxus stents, although the Endeavor stent had a significantly lower rate of stent thrombosis between one and five years [32]. The ZEST trial also showed that the Endeavor stent had better outcomes than a sirolimus-eluting stent, but similar results to a paclitaxel-eluting stent after one year of follow-up [33]. Further generations of the Resolute stent used the same cobalt-chromium platform but a polymer called biolinx consisting of a mixture of a hydrophilic component on the endoluminal surface, and a hydrophobic component on the metal surface. This polymer, which was designed to prevent thrombotic events, can release 80% of the drug within 60 days compared to a typical range of 10 to 30 days in other stents.

Everolimus is a cell cycle inhibitor. Its mechanism of action is the same as sirolimus by inhibiting smooth muscle cell proliferation. Currently available everolimus stents include the Promus (Boston Scientific, Natick, MA, USA) and Xience (Abbott Vascular, CA, USA) stents, both of which use a cobalt-chromium platform. In comparison, the Promus Element stent (Boston Scientific, Natick, MA, USA) uses a platinum chromium alloy platform with thinner struts (81 μm) than the Taxus Liberte stent (96 μm) and better deliverability. Everolimus-eluting stents have also been reported to have lower rates of ISR and repeat revascularization due to less neointimal hyperplasia than BMSs [34,35]. Compared to paclitaxel-eluting stents, everolimus-eluting stents have been reported to have better clinical outcomes at one year of follow-up [36,37], and similar clinical outcomes to sirolimus-eluting stents [35,38,39]. Another trial reported that everolimus-eluting stents were associated with a low rate of major cardiac adverse events after five years of follow-up, due to a low rate of very late stent

thrombosis [38]. Other clinical trials have reported similar results between Resolute and Xience V (Abbott Vascular, CA, USA) stents [40,41]. In summary, second generation DESs with everolimus or zotarolimus have been reported to have lower rates of very late stent thrombosis in multiple randomized controlled trials.

Novolimus is another novel drug. It is used in the DESyne (Elixir Medical, Sunnyvale, CA, USA) stent, and it is a mammalian target of rapamycin inhibitor. The thickness of the polymer coating is thinner (3 μm) than other (5–8 μm) stents, and a small randomized controlled trial reported no differences in results between novolimus-eluting and zotarolimus-eluting stents [42].

Even though BMSs are not as good as DESs, they are used in some situations. For example, the shorter duration of dual anti-platelet therapy is required with the use of BMSs due to rapid endothelialization after stenting, and they can be used in patients scheduled to undergo surgery and in those who cannot tolerate long-term dual anti-platelet therapy. BMSs have also been shown to have similar clinical outcomes in large coronary arteries (>3 mm) in terms of cardiac death and myocardial infarction compared to DESs [35].

5. Polymer-Free DESs

Theoretically, the polymer plays an important role in vessel healing. Polymer-free stents provide the benefits of vascular healing and less inflammation [43], and this may be beneficial in decreasing the rate of stent thrombosis during long-term follow-up. Therefore, it is possible that a shorter duration of dual anti-platelet therapy is safe with the use of polymer-free stents [44]. However, the problem is how to deliver anti-proliferative agents without a polymer. The function of the polymer is not only as a drug carrier, but also in controlling release of the drug. To develop polymer-free DESs, new technology was needed to allow for drug loading and released from the stent surface. Initially, direct loading of paclitaxel onto stainless steel failed to show better clinical outcomes than BMSs [45]. However, several stents were subsequently developed to achieve drug delivery without the use of a polymer. The stent surface was first modified to be porous, and then the drug was directly coated onto the stent surface by chemical bonding. Initially, nanopores (5–15 nm) were created on an aluminum stent surface. The drug was then loaded onto these pores and released after stent implantation. However, the rate of drug release was difficult to control from the nanopores.

The Yukon stent (Translumina, Hechingen, Germany) has a microporous stainless steel surface which can be coated with sirolimus. The stent should be used immediately after coating, and the drug is mostly eluted within seven days. An optical coherence tomography study of the stent coverage of the endothelium showed this stent to be better than sirolimus-eluting stents after three months [46]. Compared to paclitaxel-eluting stents, no differences in clinical outcomes were reported at five years of follow-up in the study by King et al. [47]. The ISAR-TEST 5 trial showed that this strut had non-inferior results at one year compared to a second-generation DES (zotarolimus-eluting stent) [48].

The drug can also be carried by nanoparticles in a matrix compound on a platform as used in other stents. These nanoparticles can facilitate penetration of the drug deeper into vessel walls and rapidly elute the drug. The Cre8 stent (CID Vascular, Saluggia, Italy) is a nanoparticle polymer-free stent that has an ultra-thin passive carbon coating on cobalt-chrome alloy. The anti-proliferative drug used is amphilimus, which was produced from sirolimus in a long-chain fatty acid mixture and is loaded into an abluminal reservoir. Compared to paclitaxel-eluting stents, Cre8 has shown a lower rate of in-stent late lumen loss but no difference in clinical end points [49]. The BioFreedom (Biosensors, Morges, Switzerland) stent has a stainless steel platform with a microstructure abluminal surface. Biolimus A9 is attached to the abluminal surface without a polymer. After stent implantation, one month of dual anti-platelet therapy in patients at high-risk of bleeding has shown better efficacy and safety than BMSs [44].

The Amazonia Pax (Minvasys, Gennevillieres, France) stent has cobalt-chromium platform with paclitaxel applied as microdrops on the abluminal surface by crystallization, and the drug can be released within 30 days. The VESTAsync (MIV Therapeutics, Atlanta, GA, USA) stent has a

stainless steel platform, and a hydroxyapatite surface coated with sirolimus on microporous pores. The hydroxyapatite dissolves gradually within one year. The OPTIMA (CID, Saluggia, Italy) stent has a stainless steel platform without a polymer, and tacrolimus coated into grooves as a reservoir on the stent abluminal surface.

Few randomized controlled trials have evaluated the performance of polymer-free DESs, and relevant trials on the long-term efficacy and safety compared to second-generation DESs are needed. Regarding stent technology, modification of the stent surface may influence the stent structure. The drug reservoir and release are other issues. The development of new technology and bio-materials is still needed.

6. Partially-Bioresorbable Stents

In these stents, the drug is embedded in a coating made of a bioresorbable polymer and the coating is deposited on a durable material, usually a metal. According to previous studies, stent thrombosis remains a concern after stent implantation with both BMSs and DESs. The risk factors include stent malapposition, inappropriate stent size, inadequate anti-platelet agents, delayed vessel healing, and chronic inflammation. The polymer plays an important role in the delay of vessel healing and inflammation [50,51]. No endothelial coverage of the stent surface will result in a higher rate of stent thrombosis. At least six months of dual anti-platelet therapy is currently recommended after DES implantation to decrease stent thrombosis. However, endothelial coverage can still be incomplete after six months. Even if second-generation DESs can improve vessel healing and reduce stent thrombosis, the residual polymer can still be a clinical concern. To avoid this effect, bioresorbable polymers were developed. The optimal degradation of these polymer, biocompatibility, and formulation are the most important factors in the design of bioresorbable polymers, as well as the long-term safety of the degradable compound. Several polymers are currently in use for drug elution, such as poly(D,L)lactic acid (PDLLA), poly(lactide-co-glycolide) (PLGA), and poly-L-lactic acid (PLLA). These bioresorbable polymers had better biocompatibility including endothelial function, smooth muscle cell growth, and thrombogenicity than permanent polymers such as PEVA and PBMA [52,53].

The stents that use PDLLA as the polymer include BioMatrix (Biosensor, Morges, Switzerland), Nobori (Terumo, Tokyo, Japan), Yukon Choice PC (Translumina GmbH, Hechingen, Germany), and Axxess (Biosensors, Morges, Switzerland). The stents which use PLLA as the polymer include Orsiro (Biotronik, Berlin, Germany) and DESyne BD (Elixir, CA, USA). The stents that use PLGA as the polymer include Synergy (Boston Scientific, Natick, MA, USA) and MiStent (Micell Technologies, Durham, USA). The stents that use multiple polymers include Ultimaster (Terumo, Tokyo, Japan) with mixture of PDLLA and poly(L-lactide co-e-caprolactone) (PCL), BioMime (Meril Life Sciences, Gujarat, India) with mixture of PLLA and PLGA, Combo (OrbusNeich Medical, FL, USA) with PLLA and PLGA, Infinium (Sahajanand, Gujarat, India) and Supralimus Core (Sahajanand, Gujarat, India) with mixture of PLLA, PCL, PVP, and PLGA (Summary in Table 1). According to the compound used, these polymers will biodegrade within different periods of time.

Table 1. Summary of partially bioresorbable coronary stents.

Stent	Scaffold Material	Drug	Polymer Coating	Strut Thickness (μm)	Coating Thickness (μm)	Manufacturer	Clinical Study
Axxess	Nitinol	Biolimus A9	PDLLA	152	15	Biosensors	DIVERGE
BioMime	Co-Cr	Sirolimus	PLLA/PLGA	65	2	Meril Life Sciences	meriT-1
BioMatrix	SS	Biolimus A9	PDLLA	112	10	Biosensors	LEADERS; SORTOUT VI
Combo	SS	Sirolimus	PDLLA/PLGA	100	3–5	OrbusNeich	REMEDEE
DESyne BD	Co-Cr	Novolimus	PLLA	81	<3	Elixir Medical	EXCELLA BD
Infinnium	SS	Paclitaxel	PLLA, PLGA, PCL, PVP	80	4–5	Sahajanand Mecial	SIMPLE II
MiStent	Co-Cr	Crystalline Sirolimus	PLGA	64	5/15	Micell	DESSOLVE I
Nobori	SS	Biolimus A9	PDLLA	112	10	Terumo	NEXT; SORTOUT V; COMPARE-II
Orsiro	Co-Cr	Sirolimus	PLLA	60	3.5/7.5	Biotronik	BIOSCIENCE
Supralimus	Co-Cr	Sirolimus	PLLA, PLGA, PCL, PVP	80	4–5	Sahajanand Mecial	SERIES I
Synergy	Pt-Cr	Everolimus	PLGA	74	4	Boston Scientific	EVOLVE
Ultimaster	Co-Cr	Sirolimus	PDLLA/PCL	80	15	Terumo	CENTURY II
Yukon Choice PC	SS	Sirolimus	PDLLA	87	5	Translumina	ISAR-TEST-4

Note: Co-Cr = Cobalt-Chrome; PCL = poly(L-lactide co-e-caprolactone); PDLLA = poly(D,L)-lactic acid; PLGA = poly(lactide-co-glycolide); PLLA = poly-L-lactic acid; Pt-Cr = Platinum-chrome; PVP = polyvinylpyrrolidone; SS = Stainless Steel.

Biolimus-eluting stents have showed better clinical outcomes than BMSs in patients with ST-elevation myocardial infarction [54]. In addition, they have reported to have significantly lower rates of very late stent thrombosis compared to sirolimus-eluting durable polymer stents [55,56], and non-inferior clinical outcomes to Synergy (everolimus-eluting), Nobori (biolimus-eluting), Ultimaster (sirolimus-eluting), and Orsiro (sirolimus-eluting) stents [57–63]. The Nobori stent uses the same anti-proliferative drug and stainless steel platform, but an ultra-thin non-degradable Parylene coating between the stent and bioresorbable polymer. Moreover, the SORT OUT V trial compared the Nobori stent and first generation sirolimus-eluting stents, and reported similar results at one year [64]. In addition, compared to a zotarolimus-eluting stent with a durable polymer, a bioresorbable polymer-coated biolimus-eluting stent showed similar results at 1 year of follow-up (SORT OUT VI) [65]. The Orsiro stent has an ultrathin strut (60–80 μm) with a cobalt-chromium alloy and an amorphous hydrogen-rich silicon-carbide layer, which can reduce iron release. Sirolimus is loaded onto the PLLA polymer and can be released within 12–14 weeks, with the polymer degrading within 12–24 months. The SORT OUT VII trial comparing the efficacy and safety between Orsiro and Nobori stents is currently ongoing.

Another stent uses laser drilling technology to create drug-filled holes on the stent surface. The CoStar (Conor MedSystems, Palo Alto, CA, USA) stent is made from a cobalt-chrome alloy and a bioresorbable PLGA polymer with paclitaxel. These holes can avoid long-term exposure of the polymer to the vessel wall. The COSTAR II trial reported that the CoStar stent was not non-inferior to the Taxus DES regarding clinical or angiographic outcomes [66].

In summary, partially bioresorbable polymer DESs have lower rates of very late stent thrombosis than first generation DESs, with similar results to second generation DESs. Partially bioresorbable polymer DESs have also been shown to have non-inferior results compared to second generation DESs at one year; in one meta-analysis including 11 randomized clinical trials the biodegradable polymer stents didn't show advantageous outcomes of stent thrombosis, target lesion revascularization, myocardial infarction, and cardiac death than permanent polymer stents [67]. However, further studies are needed regarding the long-term outcomes.

7. Fully Bioresorbable Stents (BRSs)

Using bioresorbable material to construct a stent is an active area of research. Bioresorbable stents are materials that can be biodegraded over time. The radial force and mechanical support are provided initially until the structure degrades. The rationale of using a bioresorbable material is to avoid the long-term development of neoatherosclerosis, stent fracture, and stent thrombosis. It can also connect native vessels to graft vessels if bypass surgery is needed. Bioresorbable material can also restore normal endothelial function in the vessels because metallic stents are not used. This new kind of stent may decrease the risk of stent thrombosis during long-term follow-up [68].

The stents are made from polymeric material, including PLLA, salicylic acid, or poly-tyrosine-derived polycarbonate and metallic material, including magnesium or zinc (Summary in Table 2). PLLA has better biocompatibility but thick struts were needed to provide mechanical strength. Thick struts may result in incomplete expansion and reduce lumen diameter. Metallic stents had better mechanical strength with thinner struts. However, magnesium had higher degradation rate and raise a problem of toxicity. Metallic Zinc is a new element for future stent design and provides low potential for restenosis and toxicity [69]. An initial clinical trial of a scaffold with magnesium reported a high restenosis rate due to the unstable release of the drug, however the later BIOSOLVE-1 trial reported better results [70,71]. The DREAMS (Biotronik, Bülach, Switzerland) scaffold uses an absorbable magnesium alloy with paclitaxel. The absorption process is complete after 9–12 months. There is a 1 μm absorbable PLGA polymer on the scaffold surface to carry the anti-proliferative drug. The DREAMS 2G (Biotronik, Bülach, Switzerland) scaffold is a next generation scaffold that uses sirolimus elution with a PLLA polymer. The structure is also made from an absorbable magnesium alloy, with fluoroscopic markers at both distal and proximal ends. The magnesium alloy

is metabolized to hydrated magnesium oxide and magnesium phosphate which can be absorbed by the body. The non-randomized BIOSOLVE-II trial showed its safety and efficacy at six months of follow-up [72].

Table 2. Summary of fully bioresobable coronary stents with Conformite′ Europe′ enne.

Stent	Scaffold Material	Drug	Polymer Coating	Strut Thickness (μm)	Manufacturer	Clinical Study
DREAMS	Mg	Paclitaxel	PLGA	125	Biotronik	BIOSOLVE-1
DREAMS 2G	Mg	Sirolimus	PLLA	150	Biotronik	
Absorb BVS	PLLA	Everolimus	PDLLA	156	Abbot Vascular	ABSORB
DESolve	PLLA	Myolimus	PLLA	150	Elixir Medical	DESOLVE
DESolve 100	PLLA	Novolimus	PLLA	100	Elixir Medical	

Note: Mg = Magnesium; PDLLA = poly(D,L)-lactic acid; PLGA = poly(lactide-co-glycolide); PLLA = poly-L-lactic acid.

The radial force of a BRS is weaker than a DES, so the recoil can be a problem because of the rapid absorption [73]. To overcome this problem, the stent design requires thick struts to maintain the radial strength. The DESolve (Elixir Medical, CA, USA) stent was made from PLLA. The eluting drug as myolimus is resorbed within 1 year, and the radial strength can be maintained for 3–4 months. A small trial showed its safety and efficacy at one year of follow-up [74]. Newer DESolve stent decreased strut thickness to 100 μm and used the drug of novolimus. Another absorbable material is PLLA known as the "Bioresorbable Vascular Scaffold" (BVS; Abbot Vascular, CA, USA) with everolimus. The thickness of the scaffold is 150 μm. An initial trial reported a low rate of major cardiac adverse events at four years of follow-up [68,75]. Compared to everolimus-eluting stents, the BVS was reported to have non-inferiority results at one year of follow-up but a higher rate of subacute thrombosis, which may be due to greater strut thickness [76,77]. One meta-analysis also demonstrated similar result [78].

A fully BRS is another choice of coronary artery intervention, and its use is increasing rapidly. However, further randomized controlled trials are still needed to compare the long-term clinical benefits with new DESs. Investigation of a new zinc stent is another way to provide benefits for mechanical strength and restenosis [69].

8. Conclusions

Coronary angioplasty and stent implantation are treatment options for CAD. The high restenosis rate of BMSs can be overcome by the development of new DESs. Paclitaxel and the "-limus" family can inhibit neointimal growth. However, first generation DESs have the concerns of long-term safety due to a high incidence of late and very late stent thrombosis. Second generation DESs with a thin structure, different polymers and new anti-proliferative drugs that can be quickly eluted have been shown to be effective and safe. Everolimus- or zotarolimus-eluting stents were shown to decrease the rate of very late stent thrombosis in many randomized controlled trials. Furthermore, stents with bioresorbable polymers or polymer-free structures may also improve long-term outcomes. However, further studies comparing these designs with second generation DESs are needed.

Fully BRSs are the latest innovation, and recent data show non-inferior results to second generation DESs at one year of follow-up. In the future, the long-term outcomes of CAD may be improved by different struts or materials.

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