EXPERT OPINION ON DRUG DELIVERY
2023, VOL. 20, NO. 4, 507–522
https://doi.org/10.1080/17425247.2023.2190580

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Drug loaded implantable devices to treat cardiovascular disease

Masoud Adhami[a], Niamh K. Martin[a], Ciara Maguire[a], Aaron J. Courtenay [b], Ryan F. Donnelly [a], Juan Domínguez-Robles [a,c] and Eneko Larrañeta [a]

[a]School of Pharmacy, Queen's University Belfast, Belfast, UK; [b]School of Pharmacy and Pharmaceutical Sciences, Ulster University, Coleraine, UK; [c]Department of Pharmacy and Pharmaceutical Technology, University of Seville, Seville, Spain

ABSTRACT

Introduction: It is widely acknowledged that cardiovascular diseases (CVDs) continue to be the leading cause of death globally. Furthermore, CVDs are the leading cause of diminished quality of life for patients, frequently as a result of their progressive deterioration. Medical implants that release drugs into the body are active implants that do more than just provide mechanical support; they also have a therapeutic role. Primarily, this is achieved through the controlled release of active pharmaceutical ingredients (API) at the implementation site.

Areas covered: In this review, the authors discuss drug-eluting stents, drug-eluting vascular grafts, and drug-eluting cardiac patches with the aim of providing a broad overview of the three most common types of cardiac implant.

Expert opinion: Drug eluting implants are an ideal alternative to traditional drug delivery because they allow for accurate drug release, local drug delivery to the target tissue, and minimize the adverse side effects associated with systemic administration. Despite the fact that there are still challenges that need to be addressed, the ever-evolving new technologies are making the fabrication of drug-eluting implants a rewarding therapeutic endeavor with the possibility for even greater advances.

ARTICLE HISTORY
Received 28 November 2022
Accepted 9 March 2023

KEYWORDS
Cardiovascular disease; implantable devices; cardiac patches; cardiovascular stents; vascular grafts

1. Introduction

Cardiovascular disease (CVD), which encompasses a broad spectrum of conditions affecting the heart, cardiac tissues, and supporting vessels, and is the primary cause of mortality and morbidity across the globe [1,2]. The World Health Organization (WHO) reports that CVD claims 17.9 million lives annually across the globe [3]. The most prevalent type of CVD is known as coronary artery disease (CAD), with peripheral artery disease (PAD) a secondary major public health concern worldwide [4]. It is believed that around 22% of the individuals who have CAD also suffer from PAD. This high degree of association between PAD and CAD is well documented [5]. As cholesterol levels rise in the body, lipids, such as low-density lipoproteins, build under the endothelium layer of the arterial wall, marking the onset of atherosclerosis [6]. As plaques accumulate in the peripheral arteries, blood flow is reduced to the body's extremities. This results in low-level tissue hypoxia, impaired endothelial function of the blood vessels, inflammation, and oxidative stress [7]. Preventative interventions are often advised to be implemented early in life since risk factors for CVDs, such as atherosclerosis, begin to manifest at a young age. It is therefore crucial to focus more on adopting good lifestyle behaviors such as regular appropriate exercise, balanced dietary habits, and through reducing exposure to respiratory pollutants such as tobacco smoke [8]. Both CVD and PAD exhibit similar pathological progression, which, accompanied with their associated morbidity and mortality rates, has prompted significant pressure to treat patients to prevent decline. Pharmacotherapy and surgical interventions are most common, with coronary artery bypass grafting and bypass graft surgery and percutaneous endovascular therapies such as balloon angioplasty or stenting common management strategies [9,10]. This review will outline drug-eluting medical implants used to treat CVD. The three main types of drug-eluting implants described in the literature for this purpose are as follows: drug-eluting stents, vascular grafts, and cardiac patches.

Drug eluting stents are implanted using percutaneous interventions (PCI). PCI is a technique that is used in the treatment of an expanding range of these diseases and was initially performed with balloon angioplasty alone [11,12]. Original procedures involved expanding a balloon of low burst pressure within the artery, and subsequently removing it once the artery lumen had been mechanically opened [13]. This type of intervention was first performed in 1977 by Dr. Andreas Grüntzig [9]. However, after plain balloon angioplasty, it was observed that up to 10% of the patients experienced vascular recoil post-intervention. Moreover, up to 30% of the patients who underwent balloon angioplasty suffered restenosis in less than 6 months post-intervention [14,15]. To address this issue, bare-metal stents (BMS) were developed to prevent blood vessel recoil [15]. Stents were designed to maintain the patency of blood vessels, and their superior performance over balloon angioplasty has been demonstrated [16,17]. However, despite its success, up to 30% of the patients treated with bare-

CONTACT Juan Domínguez-Robles jdominguez6@us.es Department of Pharmacy and Pharmaceutical Technology, University of Seville, Seville, Spain; Eneko Larrañeta e.larraneta@qub.ac.uk School of Pharmacy, Queen's University Belfast, Belfast, UK

Article highlights

- When it comes to the treatment of chronic conditions, drug-eluting implants have the ability to provide uninterrupted, long-acting systemic delivery of a wide variety of medications.
- Investigation on the use of drug-eluting implantable devices for the treatment of cardiovascular diseases has taken place throughout the last several years. The three main types of drug-eluting cardiac implants – drug-eluting stents, drug eluting vascular grafts, and drug eluting cardiac patches – are explored in great detail throughout this review.
- Drug eluting stents, which have recently attracted interest, are clinically available and have both laboratory and clinical trials. The studies imply that these implants prevent restenosis. Long-term restenosis outcomes are improved by new biodegradable stent technologies.
- Thrombosis and intimal hyperplasia are two conditions that may be treated with drug-eluting vascular grafts. These grafts, along with their recent advancements, have been addressed both as an alternative to autologous veins and as a viable treatment for these conditions.
- It has been discussed that cardiac patches could be used to effectively regenerate heart tissue in patients undergoing treatment for cardiac illness. Drug-eluting cardiac patches can mimic the natural process of heart tissue regeneration.

metal stents suffer from in-stent restenosis. A potential solution for this is to incorporate drugs within the surface of this type of medical device. Interestingly, there is an alternative to balloons and drug-eluting stents: drug-coated balloons [18]. This type of device is used to administer anti-proliferative drugs into the vessel walls to prevent restenosis. However, this type of system will not be discussed in this review as they are not implantable devices and rather constitute a transient application.

In addition to PCI, blocked blood vessels can be treated using vascular grafts [19]. Normally, autologous arteries or veins are used to achieve this [20–22]. However, in some cases, it is not possible to collect or use autologous grafts for this aim [23]. An alternative to autologous vessels is the use of synthetic vascular grafts [24,25]. This type of device has been successfully used to replace the larger blood vessels [26]. However, the use of small-diameter vascular grafts (less than 6 mm of internal diameter) could be potentially problematic [27,28] as they tend to block due to intimal hyperplasia or thrombosis [29]. Again, a potential solution to this is the use of drug-loaded vascular grafts [30–35]. The last type of implantable devices that are used to administer sustained treatment to CVD is cardiac patch. These systems are implanted into the surface of the heart to promote tissue regeneration and maintain cardiac function, following myocardial infarction (MI) [36].

This review will cover current developments in the area of drug eluting medical devices for the treatment of CVD. The vast majority of the literature is concentrated on drug eluting vascular stents. The development, however, of drug-eluting vascular grafts and cardiac patches is growing. These three types of drug eluting implantable devices will be discussed in this review.

2. Drug eluting stents

Cardiovascular BMS is implanted during PCI to maintain the patency of blood vessels. It is estimated that stent placement takes place in more than 90% of the PCI interventions [12]. However, despite its proven efficacy, up to 30% of the patients treated with this type of medical device experience restenosis during the first 6 months after the PCI [14].

BMS are commonly made from stainless steel, cobalt chromium, or other strong, corrosion-resistant alloys [37]. However, these have been associated with adverse outcomes. Stent restenosis, the 'enemy of interventional cardiologists,' is the narrowing of stent lumen diameter post-PCI and is reported to occur in between 20% and 30% of patients treated with BMS [11,38,39]. A key process leading to in-stent restenosis is neointimal hyperplasia, which results from an exaggerated inflammatory response to stent placement due to continuing injury. Continued injury results in the proliferation of vascular smooth muscle cells (VSMCs). Clinical consequences of in-stent restenosis are the return of anginal symptoms or acute coronary syndrome. This leads to the need for re-PCI or for coronary bypass surgery [38]. To improve on these outcomes, several inorganic coatings have been tried, including titanium-nitride-oxide layering, diamond and carbon coatings, and iridium oxide coatings. Unfortunately, these coatings did little to improve outcomes [37]. Advancements in the field in the 1990s led to the production of drug-eluting stents (DESs), which has decreased the risk of restenosis to less than 10% and, therefore, drastically reduced the need for re-intervention [12,38,40]. The DES was originally designed by coating standard BMS, with a polymer coating containing an anti-proliferative agent to inhibit the proliferation of VSMCs [12,41]. Clinical use of these stents indicated that DES carried a higher risk of late (up to 1 year) and very late (beyond 1 year) thrombosis and restenosis, presenting a significant safety concern [42]. The indiscriminate nature of the anti-proliferative drugs within DES is thought to be an important factor in these outcomes as they prevent not only the proliferation of VSMCs but also endothelial cells (ECs). The EC layer traditionally exerts a protective function through the production of nitric oxide by an enzyme, nitric oxide synthase, from L-arginine. Nitric oxide is a potent inhibitor of platelet aggregation through antagonism of the thromboxane A_2 receptors, therefore playing a role in blood coagulation. It was also found to inhibit the proliferation of VSMCs in animal models, an important consideration in the process of neointimal hyperplasia. Further, nitric oxide, along with other substances produced by ECs plays an essential role in the regulation of vascular tone [43]. Inflammatory responses to polymers used have also been implicated in thrombosis and restenosis [42]. Several adaptations to this initial design were made for second- and third-generation DES in an attempt to overcome the increased risks. These included using new drugs, alternative polymer selections, and consideration of the scaffold designs. To date, selective therapeutics for VSMCs over ECs are being pursued, and so current research is focusing on overcoming these limitations [14].

2.1. Coated DES

The vast majority of the commercially available DES is composed of a metallic stent coated with drug-containing formulations [44]. There are a wide range of industrially available methods to achieve surface deposition of drug loaded

formulations on the stent surface [44]. As mentioned before, the vast majority of the literature describing drug eluting medical devices for CVD treatment are focused on DES. These works cover a wide variety of aspects from fundamental manufacturing aspects to clinical applications. The following sections will describe DES that rely on coatings in order to load drugs onto the device.

2.1.1. First generation DES

First-generation DES is typically BMS coated with non-biodegradable polymers with a thick strut that elutes sirolimus or paclitaxel. Figure 1 shows a diagram summarizing first-generation DES characteristics, materials, and drug loadings. The Cypher™ stent contains 140 mcg/cm^2 of sirolimus in a polymer matrix of poly(ethylene vinyl acetate) and poly(-n-butyl methacrylate) [46,47]. Sirolimus, along with the other 'limus' drugs, are a group of immunomodulators that inhibit the mTOR pathway causing arrest of the cell cycle in G0/G1 phases of the cell cycle in a cytostatic manner [48]. The Taxus™ stent contains paclitaxel at a concentration of 1 mcg/mm^2 in a poly (styrene-b-isobutylene-b-styrene) matrix [47]. Paclitaxel is a microtubule stabilizing agent that arrests the cell cycle primarily in the M phase [48]. Although a vast improvement in restenosis rates was achieved, the non-bioresorbable polymers in the first-generation DES were implicated in initiating inflammatory responses. This triggered safety concerns regarding late restenosis and thrombosis [49]. Furthermore, the thick strut present in the first-generation stents limited the delivery of drugs from the stent [50]. The presence of thick struts, as in first-generation DES, has been positively correlated with an increased risk of a hyper-inflammatory response leading to thrombosis and restenosis [51]. The presence of a thick strut causes downstream changes in the blood flow resulting in areas of low endothelial shear stress. These areas promote the proliferation of VSMCs, the attraction of inflammatory cytokines, and the activation of platelets in the production of cytokines [52].

2.1.2. Second generation DES

Second-generation DES is also coated with non-bioresorbable polymers but have a thinner strut and contain everolimus and zotarolimus (Figure 2) [49,53]. The polymers used were biocompatible and exhibited reduced pro-inflammatory responses [50,54]. The second-generation DES also contained newer antiproliferative drugs (everolimus and zotarolimus), which exhibited improved release kinetics [55]. The coating of these devices is normally made from poly(vinylidene fluoride-co-hexafluoropropylene) and poly(n-butyl methacrylate).

The efficacy of these systems was evaluated in different clinical trials. The SPIRIT II trial aimed to draw a comparison between the Xience V® (2nd gen DES loaded with everolimus) and Taxus Express® (1st gen DES loaded with paclitaxel) platforms. At the 5-year follow-up, this study demonstrated a significant reduction in cardiac mortality in the Xience V® (2nd gen DES loaded with everolimus) platform along with a sustained reduction in cardiac death (CD), MI, and ischemia-driven target lesion revascularisation (TLR) rates [56]. The SPIRIT III trial, a larger randomized controlled trial, further confirmed these findings at 5 years follow-up post-intervention. It identified a significant reduction in target lesion failure rates (TLF) (encompassing CD, target vessel MI, and ischemia-driven TLR) and major adverse cardiac events (including CD, MI, and ischemia-driven TLR) between the Xience V® and Taxus Express® stents. However, the 5-year post-intervention follow-up of SPIRIT III found no superiority in the Xience V® stent for MI, stent thrombosis, and ischemia-driven TLR [57]. A two-year follow-up of a larger-scale study, SPIRIT IV, concluded that there was a significant reduction in TLF, which included CD, target vessel MI, and ischemia-driven TLR, as well as in thrombosis rates and all-cause MI

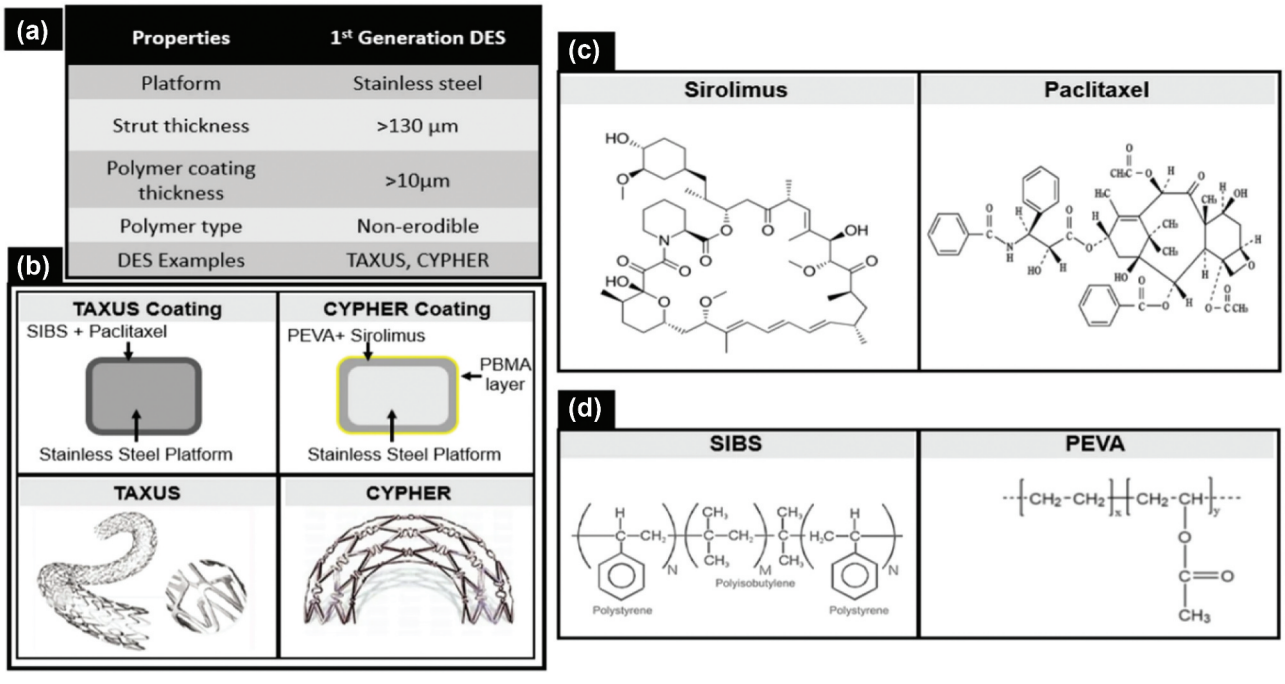

Figure 1. Characteristics of 1st generation DES: properties (a), Design and structure (b), drugs (c) and materials (d). Reproduced with permission from Hassan et al. [45].

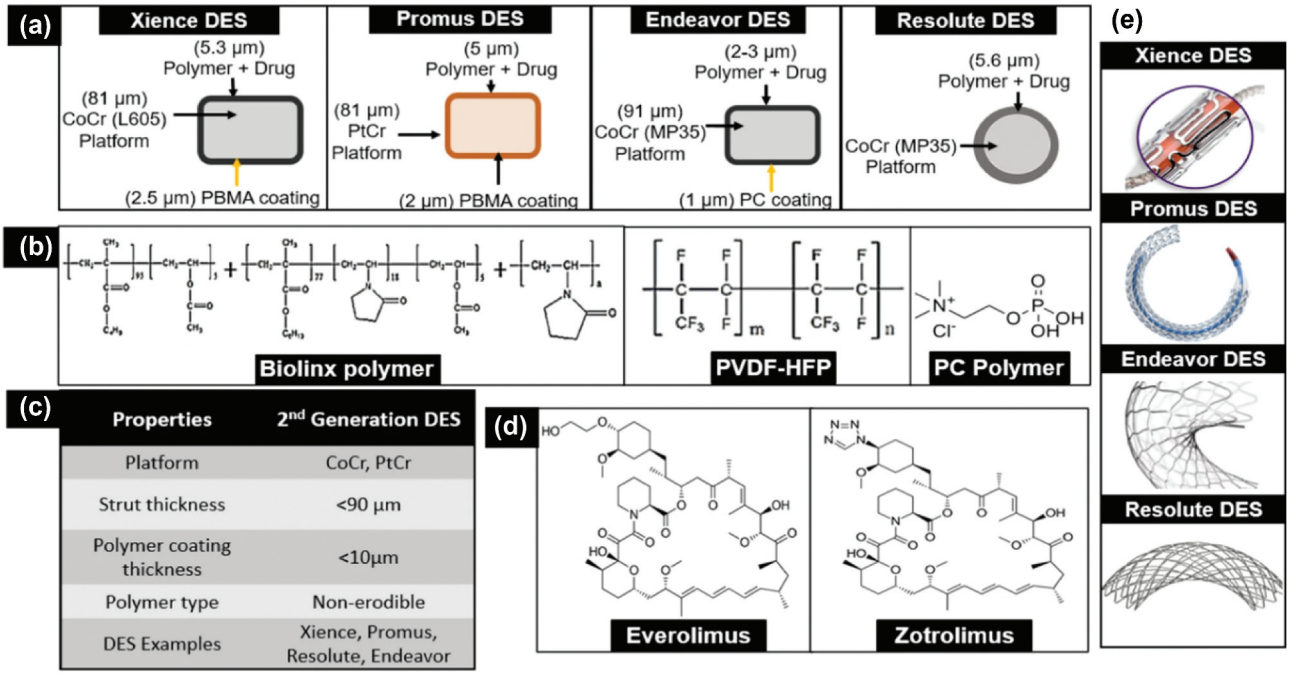

Figure 2. Characteristics of 2nd generation DES: structure (a), materials (b), properties (c), drugs (d) and design (e). Reproduced with permission from Hassan et al. [45].

between the Xience V® and Taxus Express® stents [58]. The 5-year post-intervention follow-up for the RESOLUTE-all corners trial compared the Resolute® (2nd gen DES loaded with zotarolimus) to the Xience-V® stent and found no significant difference in patient-related outcomes (all-cause mortality, MI, and all-cause revascularisation), device-related outcomes (CD, target vessel MI, and clinically indicated TLR), major adverse cardiac events (all-cause death, MI, emergency coronary bypass, or clinically indicated TLR), and stent thrombosis rates [59].

2.1.3. Third generation DES

The use of non-bioresorbable polymers in the first- and second-generation stents is correlated with an increased risk of late thrombosis compared to the original BMS. The non-bioresorbable polymers delay the healing of arteries and cause pro-inflammatory and hypersensitivity reactions [49,60–62]. The use of bioresorbable polymer coatings on metal stents indicated the beginning of third-generation DES, which aimed to overcome these issues [49,61]. Once the drug has been fully eluted and anti-proliferative effects gained, the polymer coating on the metal stents fully degrades leaving essentially a BMS (Figure 3). This allows for re-endothelialisation and therefore reduces the risk of inflammatory reactions [60,61].

Biomatrix®, Nobori®, Axxess®, Supralimus®, Infinnium®, Biomine®, Orsiro®, Desyne®, Synergy®, Mistent®, FireHawk®, and bioMime® are all third-generation DES that have CE markings, showing they meet the standards required by the European economic area [64–68]. The third-generation stents appear comparable to durable polymer-coated stents in many trials. However, there may be some benefit in preventing stent thrombosis, however longer-term studies are still needed to confirm this [61].

The Synergy® stent platinum-chromium alloy platform is coated with poly(lactic co-glycolic acid) loaded with everolimus [61]. Everolimus is eluted from the stent over approximately 90 days, with complete polymer degradation occurring after 120 days post-implantation [69]. The efficacy and safety of the Synergy® stent, in comparison with the durable polymer DES, were largely established through the EVOLVE trials [70]. EVOLVE was the original trial comparing TLF rates (encompassing CD, target vessel MI, and clinically indicated TLR) at 30 days to the Promus® stent () [71]. The 5-year follow-up to the EVOLVE trial concluded non-inferiority in the TLF rates [72]. The EVOLVE II clinical trial had a primary endpoint of non-inferiority between the Synergy® (3rd gen DES loaded with everolimus) and Promus® stents (2nd gen DES loaded with everolimus) of TLF rates (encompassing ischemia-driven TLR and MI in the target vessel and death related to the target vessel). The original study found no significant difference between the two stents. The 5-year follow-up, published in 2019, sustained these findings and indicate no significant difference in any of the individual outcomes assessed within TLF rates [69].

The Orsiro® stent consists of three layers. The innermost cobalt chromium platform is covered by a thin coating of silicon carbide to reduce the allergic reaction caused by metal ions being in contact with blood and vessel walls. Finally, the rate-controlling poly-L-lactic acid (PLLA) matrix contains the anti-proliferative drug sirolimus. The thickness of this rate-controlling polymer layer is thicker (7.5 μm) on the abluminal side in comparison to the luminal side (3.5 μm). PLLA undergoes a hydrolytic reaction, with drug elution occurring for 12–14 weeks post-implantation. The Orsiro® stent was evaluated against the Xience® (2nd gen DES loaded with everolimus) stent in the BIOFLOW trials. BIOFLOW II, a randomized controlled trial, assessed late lumen loss (LLL) as a primary

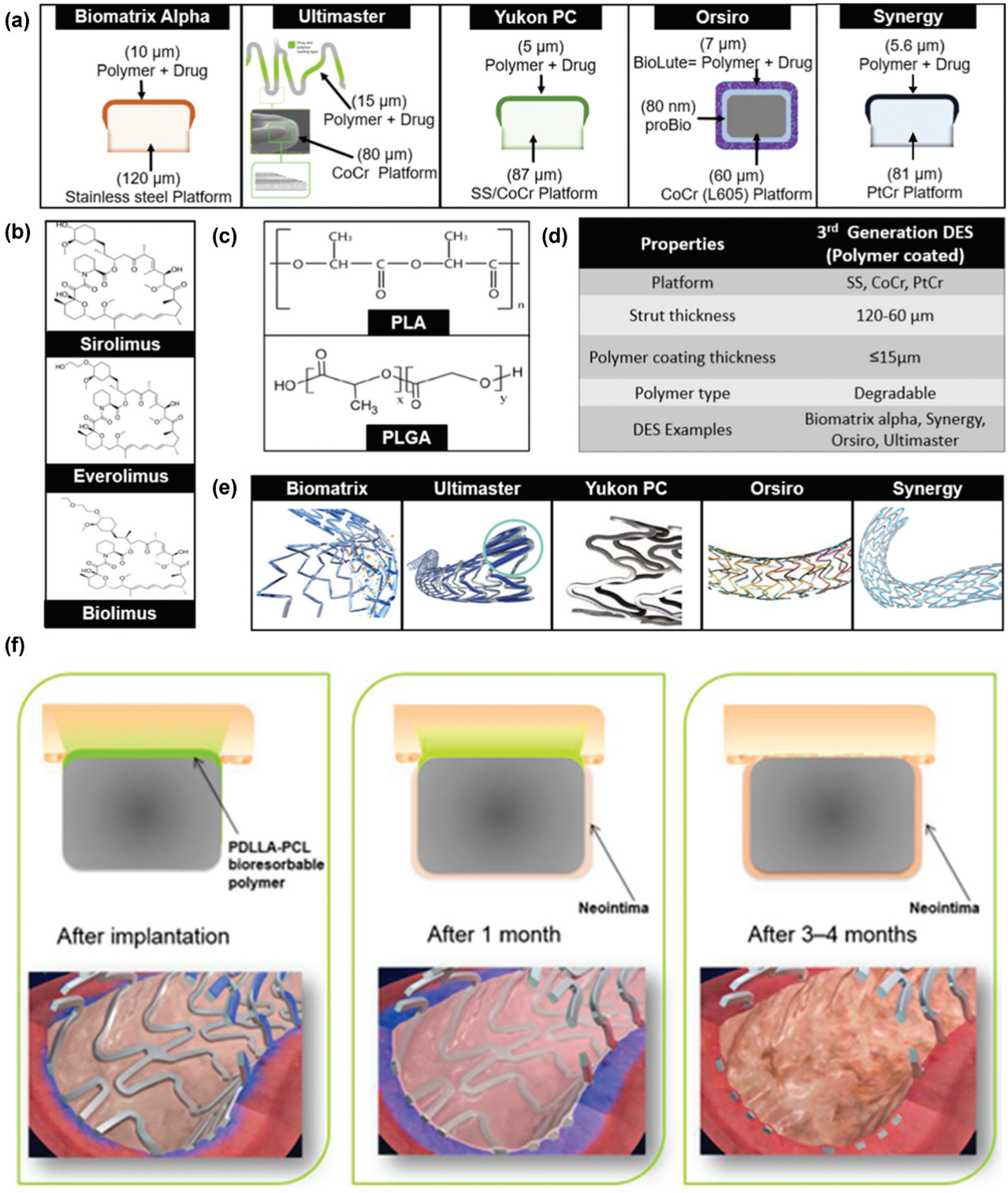

Figure 3. Characteristics of 3rd generation DES: structure (a), drugs (b), materials (c), properties (d), design (e) and polymer degradation after DES implantation (f). Reproduced with permission from Hassan et al. and Chisari et al. [45,63].

endpoint and after 9 months showed non-inferiority compared to the Xience® stent. The BIOFLOW VI trial also concluded that, at 9 months, LLL was non-inferior to the Xience® stent [73]. The BIOFLOW IV trial compared TVF rates (includes CD, Q-wave or non-Q-wave MI, emergency coronary artery bypass, or clinically driven target vessel revascularisation) of the Orsiro® stent to the Xience® stent (2nd gen DES loaded with everolimus) and concluded that it was comparable [73,74]. Moreover, TLF rates (a combination of cardiac death, MI in the target vessel, and clinically indicated TLR) of the Orsiro® stent were assessed in the 5-year follow-up to the BIOFLOW II trial and BIOFLOW V trials compare to those of the Xience® stent (2nd gen DES loaded with everolimus) at 60 and 12 months, respectively [73,75]. The 5-year follow-up of the BIOFLOW II study concluded non-inferiority. Promising results were obtained in the BIOFLOW V trial as superior rates of TLF rates were found at 12 months and the statistical significance of these results was

increased as the authors of BIOFLOW V included results from the 5-year follow-up of BIOFLOW II in a Bayesian analysis [73].

2.1.4. Dual-DES

Dual DES has been designed to overcome delayed re-endothelialisation, restenosis, and thrombosis associated with DES. Several drug combinations have been used including combinations of anti-proliferatives, anti-inflammatories, anti-thrombogenics, and immunosuppressants. The Cilotax® stent contains a combination of cilostazol and paclitaxel [76,77]. Cilostazol has antiplatelet effects as well as anti-proliferative effects on VSMCs. The effect of this was evaluated in a small trial with the Taxus® stent. The study showed promising results: late in-stent loss and restenosis were significantly lower in the Cilotax® group and thrombosis did not occur in either group [78]. Other drugs which promote the re-endothelialisation of the stent have also been included in dual-DES in order to prevent thrombosis associated with anti-proliferative DES [76]. Further, the inhibition of EC is implicated in late restenosis seen with DES as an endogenous substance produced by ECs, nitric oxide, and inhibits VSMC proliferation [43]. One such example is the incorporation of estradiol into a sirolimus-containing stent [76,77]. Estradiol exhibits a number of vasculoprotective effects by inhibiting VSMCs proliferation and promoting EC proliferation. The ISAR-PEACE randomized control trial sought to evaluate the effect of this compared to a sirolimus-only DES but failed to prove any benefit [79]. The Combo® stent, which has obtained CE marking in Europe, is a polymer-free DES coated with sirolimus and CD34+ antibodies [77,80]. The stent used 'capture technology' for endothelial progenitor cells, which bind to CD34+ antibodies and rapidly re-endotheliase the stent surface [81]. Pooled analysis of one-year post-intervention outcomes from the MASCOT and REMEDEE trials concluded that the safety profile of the combo stent was, 'excellent' in comparison to some of the newer DES. A comparative study between Orsiro® (3rd gen DES loaded with sirolimus) and Combo® stents (dual-DES loaded with sirolimus and antibodies), the SORT OUT X trial [82].

This trial suggested that Orsiro® performance was superior to the Combo® stent. The latter was associated with a higher risk of the revascularisation of the target lesion.

In addition to the dual-DES used clinically, researchers are currently developing new types of dual-DES [76,77]. Wang et al. described the use of an electrospinning coating technique to add sirolimus and an antioxidant molecule, 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl, to the surface of metal stents [83]. The combination of sirolimus and the antioxidant showed rapid endothelialisation in a porcine animal model. Moreover, the resulting dual-DES showed anti-stenoic effects. Alternative approaches have also been described such as the use of sirolimus combined with a coating capable of releasing nitric oxide. This compound has proven to be effective in promoting arterial healing [84]. For this purpose, Zhang et al. developed a new coating containing sirolimus and immobilized bivalirudin using a network of epigallocatechin gallate and copper ions [84]. This coating was capable of generating nitric oxide. In vivo results using an animal model suggest that this DES prevented restenosis while promoting endothelial regeneration.

2.1.5. Triple DES and MicroRNA (miRNA) delivery systems

Triple DES contains three different active compounds. A good example of this type of devices was proposed by Hu *et al., who* produced a triple DES by spraying multiple atomized layers onto a BMS. The first ultrasonically atomized layer sprayed onto the BMS was hydrophilic chitosan containing SZ-21, a monoclonal antibody against platelet aggregation, and vascular endothelial growth factor (VEGF), a proangiogenic factor that promotes endothelialization. The second hydrophilic layer contained PLLA and sirolimus to prevent hyperplasia of the arterial walls. The authors report a good release profile, good hemocompatibility, and anti-inflammatory properties [85]. Similarly, Cheng et al. described a triple DES loaded with heparin as the anticoagulant, VEGF, and sirolimus [86]. These compounds were coated into a BMS using a combined methylacrylated gelatin-poly(ethylene glycol)/poly(caprolactone) matrix. In vitro tests showed sustained release of heparin-VEGF and sirolimus. Moreover, the resulting stents showed anticoagulant properties. Finally, the efficacy of this type of device was tested using a rabbit animal model reduced in stent restenosis.

The current drugs used in DES are indiscriminate between VSMCs and EC. To overcome these shortcomings, microRNA-based therapy has been investigated to allow the proliferation of EC and selectively hindering inflammatory cells and VSMCs [14]. miRNA-21, miRNA-146, miRNA-221/222, miRNA-424, and the miRNA17–92 cluster have all been identified as upregulated following implantation of stents and promotes the proliferation of VSMCs. The proliferation of VSMCs plays a vital role in stent neointimal hyperplasia and, therefore, restenosis formation. Further, miRNA-126 and miRNA-92a, which are both involved in EC proliferation, are both downregulated in response to stent placement [87]. Santulli *et al.* designed an adenoviral vector that would allow a selective proliferation of EC and not VSMCs if delivered *via* a stent. The vector encoded P27, a cell cycle inhibitor, and four complementary sequences of miRNA-126-3p, which is highly expressed in ECs and regulates vascular integrity and angiogenesis. Therefore, when present in ECs, the overexpression of P27 should not take place due to complementary base pairing with endogenous miRNA126 resulting in degradation or inhibition of translation, as it does in VSMCs. The authors noted that during two- and four-week post-implantation into an animal model, complete re-endothelialisation, reduced restenosis, hypercoagulability, and restoration of the vasodilatory response to the neurotransmitter acetylcholine occurred [88].

2.2. Other types of DES

As an alternative to metallic stents coated with drug containing formulations, polymeric stents have been developed. Stents can be manufactured using a wide variety of polymers, but normally they are prepared using bioresorbable polymers such as poly(lactic acid), poly(caprolactone) or poly(lactic-co-glycolic acid). In this way, the polymer can be combined with the drug to form a drug loaded matrix. The stent can be prepared using micro-injection molding techniques or using laser cutting [89]. In addition to these types of technologies, the use of 3D printing for DES manufacturing is

gaining attention due to its versatility [89]. However, most of the studies describing the use of 3D printing for stent manufacturing do not include the drug within the matrix but rather coated at the surface of the device.

2.2.1. Biodegradable DES

The use of biodegradable DES offers several advantages over conventional stents. The presence of metals or polymers in the blood vessels can initiate an inflammatory response, prevent healing, and can cause endothelial dysfunction. These outcomes have been linked to the late thrombosis restenosis occurrence in DES [42]. Furthermore, loss of vasomotion, problems in revascularisation of the target vessel, and stent fracture can all occur [54]. Non-bioresorbable stents also limit the use of magnetic resonance imaging, whereas bioresorbable seems to be compatible with MRI and computed tomography imaging, which can hold an important place in diagnostics [54,90]. The use of bioresorbable stents also allows for the recovery of vasomotion, an important process in tissue perfusion, and the possibility of positive remodeling [91,92].

Four of the bioresorbable stents currently comply with European legislation and have received the CE marking; the DeSolve® Novolimus®, Fantom®, ART®, Fortitude®, and Magmaris® stents [93,94]. The Absorb® BVS 1.1 had previously gained its CE marking but was pulled from the market in 2017 due to potential safety concerns [94,95]. There have been several randomized controlled trials assessing the Absorb® stent: ABSORB I-IV, ABSORB CHINA, ABSORB JAPAN, and AIDA. A pooled analysis of the results has been performed, and it concluded that the BVS arm of the studies was more at risk of target vessel failure and device thrombosis [94]. Reva developed the Fantom® sirolimus-eluting stent whereby 60% of the sirolimus contained is released within 30 days post-implantation. The scaffold degrades over 36–48 months. The FANTOM II trial found the LLL in the Fantom® stent after 6 months to be comparable with 'contemporary metallic DES' and also with other bioresorbable stents. Furthermore, the study revealed major adverse cardiac events (CD, MI, and clinically indicated TLR) rates of between 2.6% and 2.8% at 6 months compared to rates of 3–5% with other bioresorbable stents [96]. The ART Pure Resorbable Scaffold® stent is completely bio-absorbed within 18 months. The stent has been evaluated in the ARTDIVA trial, a single-armed first-in-man study; however, no official results are published [54,93,97]. The Desolve® stent contains novolimus of which 85% is released over 4 weeks and fully resorbed over 2 years [98]. A 2-year follow-up to the first in man study for the Desolve® stent reported a LLL equal to that of current bioresorbable stents and DES along with equal efficacy to the Absorb® stent but with a quicker resorption time allowing for positive vessel remodeling [99]. Approximately 95% of resorption of the Magmaris® bioresorbable scaffold occurs within 12 months [100]. The Magmaris® stent first in man study was the BIOSOLVE II trial. The three-year outcomes report TLF and clinically indicated TLR rates similar to those obtained with the Xience® stent and no incidences of thrombosis were reported [101]. Although bioresorbable stents, in theory, offer numerous advantages over DES, the clinical trials conducted have presented mixed results and there is a lack of comparative trials with other generation stents [102].

3. Cardiovascular grafts

Coronary artery bypass graft surgery (CABG) is one of the most common treatments for CVDs. It is performed to restore blood flow and oxygen delivery by rerouting blood around restricted or obstructed arteries. A blood vessel is taken from one section of the body and linked to the coronary artery above and below the constricted area in order to restore blood flow to the heart. Vascular grafts are used extensively across the globe, with many surgeons' preferred graft for the majority of vascular bypass surgeries being autologous vascular tissue. The merits of autologous tissue include a live, non-thrombogenic endothelium, being biocompatible, and good surgical handling properties. The use of autologous arteries, such as the radial artery, internal thoracic artery, and saphenous vein, is considered to be the gold standard for CABG surgery [103]. On the other hand, a significant number of

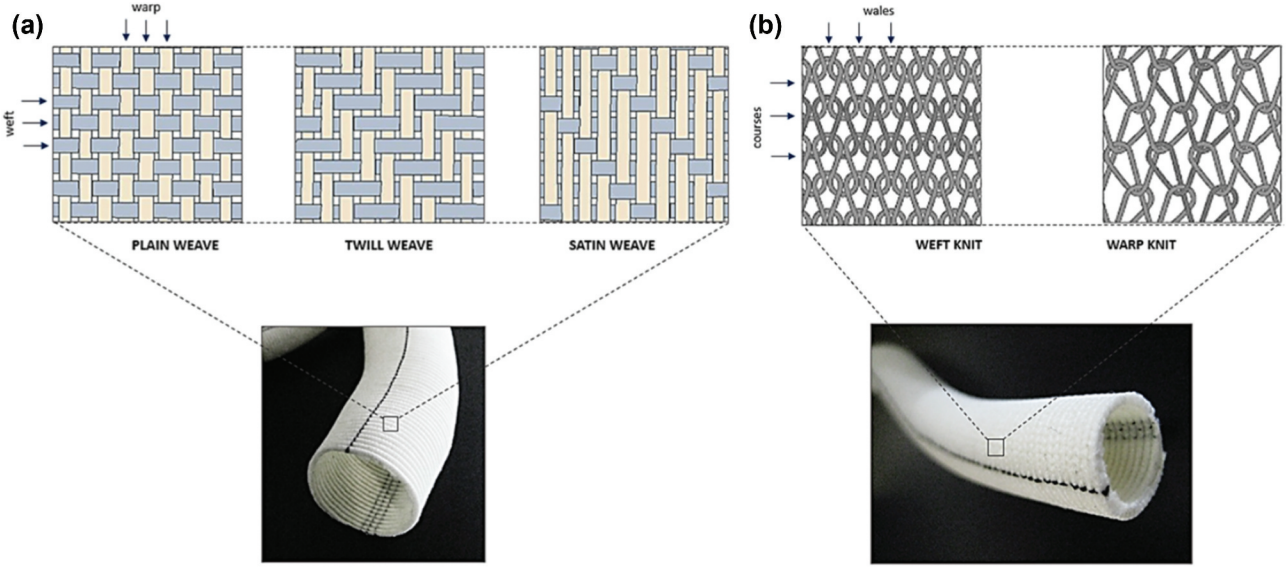

Figure 4. Dacron vascular grafts: woven structure (a) and knitted structure (b). Reproduced with permission from Singh et al [105].

patients lack appropriate donor tissue because of a preexisting illness or tissue removal from prior procedures. In these situations, surgeons should use artificial vascular conduits like poly(ethylene terephthalate), also known as Dacron® or expanded poly(tetrafluoroethylene) (ePTFE) also known as Gortex® [104]. Figure 4 shows an image of Dacron vascular grafts showing different structures. Even though Dacron® and Gortex® grafts are readily available and have been shown to be effective in clinical settings for some applications, there is still a lot of potential for improvement. The outcomes of using synthetic vascular grafts to bypass small-sized arteries (less than 6 mm in diameter) have been consistently dismal, with reported patency rates of just 40% after 6 months and 25% after 3 years [106]. These smaller conduits cannot be used in CABG or distal lower limb revascularisation treatments because they are more likely to fail as a result of secondary clot formation or intimal hyperplasia. To prevent restenosis and neointimal hyperplasia, anti-migratory and antiproliferative were administered systemically; however, this did not result in effective clinical outcomes. Due to these problems associated with bypasses, incorporation of drug into grafts providing a local delivery system is necessary as it is without systemic side effects and provides safe delivery of the drug to treat CVD. Ideal vascular graft systems would prevent pathologies such as neointimal hyperplasia and thrombosis but also allow endothelialisation to occur. Given the prevalence of vascular disease, it is evident that a small-diameter vascular graft with outcomes that are on par with those of autologous vessel bypass surgeries is needed.

Vascular grafts have been extensively described in the literature, and they are currently being used to treat patients. The use of drug-eluting vascular grafts, however, is not as extended. This area of research is gaining momentum, and multiple publications can be seen focusing on new manufacturing methods for this type of device. This section summarizes the recent progress in the development of drug eluting small-diameter vascular grafts. In addition, it provides an overview of the two different popular techniques that are being used to fabricate such vascular grafts. The majority of these works are focused on optimizing manufacturing conditions and in some cases testing these devices using animal models. These manufacturing techniques include electrospinning and 3D-printing.

Electrospinning is a versatile technology that can yield nanofiber material. With electrospinning, it is possible to manufacture interconnected structures that are porous with desirable characteristics such as desirable morphology, high permeability, and a high surface-to-volume ratio. It is one of the most promising manufacturing methods for producing polymeric matrices that resemble the extracellular matrix organization, such as blood vessels [107]. Important tailorable parameters in electrospinning include polymer selection (molecular weight), solvent and solution concentrations and viscosity, applied voltage, flow rate, Taylor cone-to-collector distance, collector design, and environmental conditions like humidity, temperature, and air velocity. Specific selection and optimization of each of these are needed to ensure the final product meets the desired target profile [107]. By optimizing the process parameters, a fabric may be produced from dry polymer fibers with diameters ranging from 50 nm to 20 µm, which is smaller than those produced by the vast majority of currently known fiber spinning methods [108]. One of the limitations of this manufacturing method is that, in some cases, the use of organic solvents is required. The use of these solvents could present toxicity issues and therefore residual solvent content in vascular grafts prepared using this technique should be monitored.

In a study carried out by Nourozi *et al*., the researchers developed a bi-layered vascular graft that was loaded with heparin and was constructed of poly(caprolactone) (PCL) and gelatine [109]. These bi-layer vascular grafts were prepared by electrospinning and freeze-drying technology. Their mechanical strength was determined to be comparable to that of the coronary artery. Moreover, according to this study's findings, the addition of heparin led to an improvement in the attachment of endothelial cells and a reduction in the number of activated platelets [109].

In a separate study, Hu and colleagues investigated the use of electrospun PCL/collagen/elastin-based conduits as vascular grafts loaded with heparin and VEGF [110]. PCL/collagen/elastin conduits (with heparin and VEGF) demonstrated a better effectiveness of vascular regeneration without thrombus formation when compared to electrospun PTFE (ePTFE) grafts that did not include VEGF and heparin (Figure 5) [110]. Shitole et al. synthesized nanofibrous scaffolds using an electrospinning method after successfully incorporating clopidogrel into a poly(urethane)/poly(ethylene glycol) (PU/PEG) polymeric mixture solution. The electrospun PU/PEG/clopidogrel scaffolds demonstrated hemocompatibility as well as antithrombogenic capabilities, allowing them to be used as a blood-contacting antithrombotic material [111].

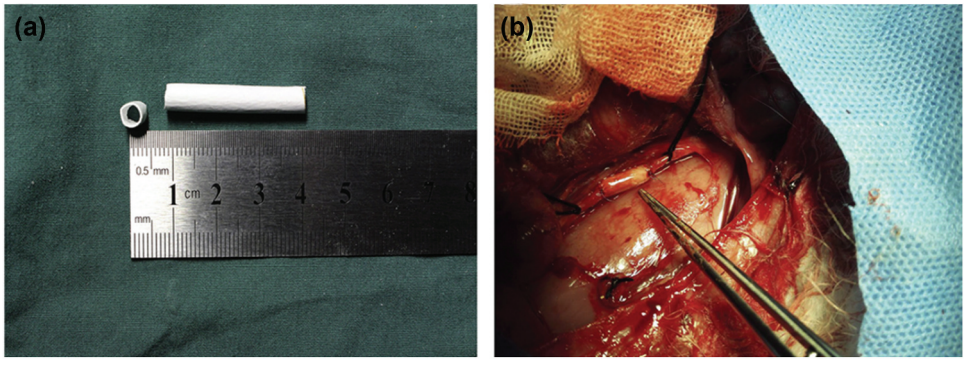

Figure 5. ePTFE electrospun vascular graft loaded with heparin and VEGF (a). Vascular graft implantation in the intrarenal aorta of a rabbit model (b). Reproduced with permission from Y.-T. Hu et al. [110].

In 2021, Serpelloni *et al*. produced a chitosan-based nanofiber coating (CNC) of vascular grafts that releases the antibiotic vancomycin. The nanofiber outside is used to prevent infection when the grafts are implanted by sustained release of vancomycin as the wound is healing following implantation. This is in response to the systemic administration of antibiotics failing to prevent infection. Vascular graft implantation without antibiotic treatment following can cause major complications such as sepsis and even death. The CNC was produced from a mixture of chitosan nanofibers, poly (vinyl alcohol), and vancomycin. The preliminary results obtained from this study so far show the sustained and local deliveries of antibiotics to prevent infection associated with bypass surgery [112].

In addition to electrospinning, drug eluting vascular grafts have been prepared using 3D printing technologies. It is an exciting and growing method to make novel implantable drug delivery systems. Additive manufacturing commonly produces devices in which the drug is dispersed throughout (matrix-type implants). However, there are limitations to this method as some drugs cannot withstand the high temperatures and solvents involved [113].

In 2021, Domínguez-Robles et al. [35] produced vascular grafts from PCL loaded with dipyridamole (DIP) (Figure 6). DIP was chosen as it is an anticoagulant used to provide antithrombosis and in addition has shown promising results in promoting the proliferation of vascular endothelial cells and reducing smooth muscle cell proliferation. PCL and DIP were mixed in the absence of solvents, and the grafts were 3D printed. In order to ensure integration of the DIP in the matrix, both high and low molecular-weight PCL were used. 3D printing was chosen to allow the production of precise and highly customizable structures. Full characterization of the vascular grafts produced was carried out, additionally evaluating drug release, antiplatelet effect, and cytocompatibility. From these characterization procedures, it was shown that DIP had a sustained and linear drug release profile without any initial burst for 30 days. It was also shown that DIP was well integrated into the PCL matrix, which can be explained by hydrogen bonding occurring between the polymer matrix and the drug. The results showed that DIP provided a clear reduction in platelet deposition when compared to PCL alone. The higher percentage of DIP grafts produced (20%) had a low rate of hemolysis and also allowed cellular attachment, viability, and growth. However, further evaluation of the use of grafts *in vivo* is required by carrying out animal studies. Additionally, sterilization techniques are needed before this device is efficiently evaluated [35].

In another study by J. Domínguez-Robles et al. [32] fused deposition modeling (FDM) technology was used to fabricate thermoplastic polyurethane (TPU) based vascular grafts loaded with DIP. These authors reported that high drug loadings did not result in a reduction in platelet adhesion due to surface properties. Additionally, graft fidelity after printing was compromised by high drug loading (Figure 6a-d). Finally, it was concluded that 5% DIP loading was ideal for preventing platelet adhesion while keeping a good printability. The authors reported that the resultant grafts are able to provide a sustained release of DIP over a period of 30 days without any sign of burst release. In addition, all of the 3D-printed materials generated in this study were shown to be cyto- and hemocompatibility. Moreover, the grafts with lower DIP cargo were reported to enhance the proliferation of HUVEC cells. Finally, in this study, Dominguez-Robles et al. showed the versatility of 3D-printing to prepare double layered small-diameter vascular grafts, which contain rifampicin (RIF) and DIP (Figure 6e-f). This type of technology can be used to prepare advanced devices to address multiple problems. In this case, loading antibiotics and antiplatelet drugs can be used to prevent blood clot formation and infections.

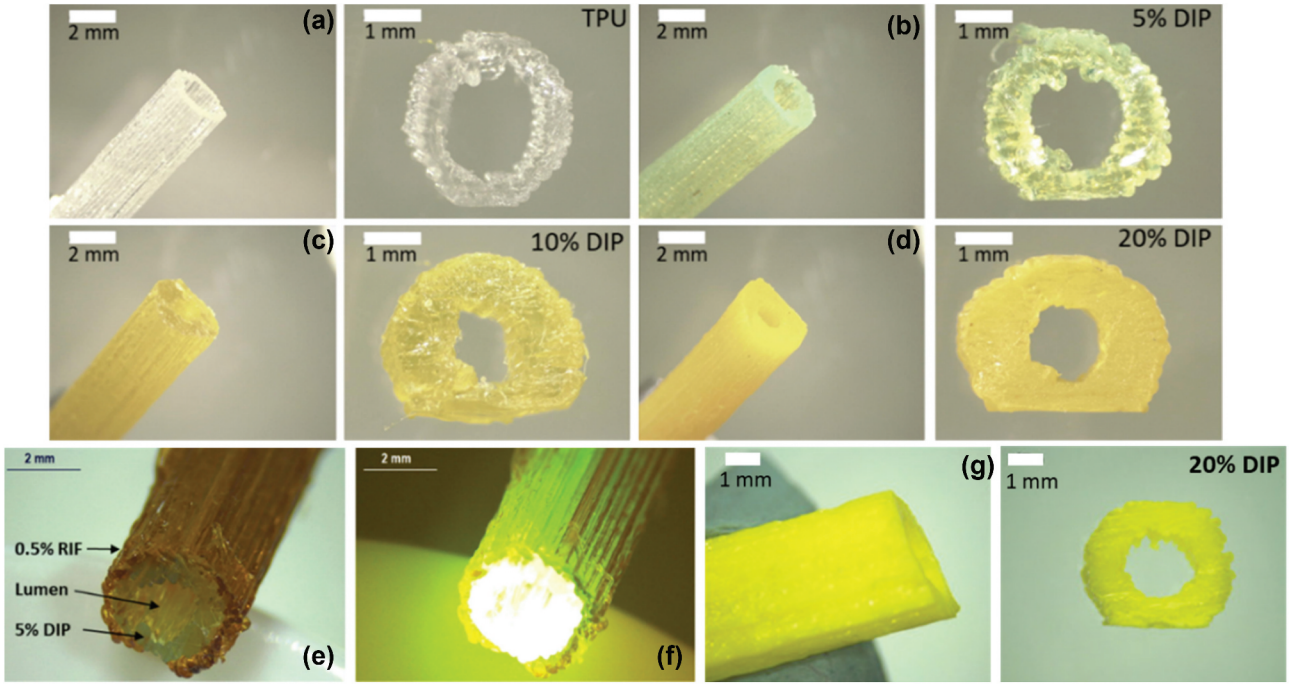

Figure 6. Drug loaded vascular grafts prepared via-3D-printing: TPU vascular grafts loaded with different amounts of DIP (a-d); dual vascular grafts loaded with RIF and DIP (E and F); PCL vascular graft loaded with 20% DIP. Reproduced with permission from J. Domínguez-Robles et al. [32,35].

In a separate study, Jia et al. [114] produced vascular grafts using a multilayer co-axial nozzle system. Human umbilical vein endothelial cells (HUVECs) and mesenchymal stem cells (MSCs) were also multiplied and encased in a bioink made of gelatin methacryloyl (GelMA), 4-arm poly(ethylene glycol)-tetra-acrylate (PEGTA), and sodium alginate. Highly ordered vascular systems were printed using the existing bioprinter setup and the produced bioink. After 21 days, the cells had completely filled the 3D-printed vascular grafts with no cytotoxicity noted. Immunofluorescence was used to better understand how cells behaved inside the vascular wall. The results revealed that MSCs and HUVECs both expressed the proteins –SMA and CD31 in a constructive fashion.

The studies and information in this paper show that vascular grafts have major potential in the treatment of cardiovascular vascular disease. There are, however, many aspects that should be addressed before these devices can be clinically applied. To start, many of the works described here proposed the use of biodegradable vascular grafts. These devices aim to deliver drugs and to act as scaffolds for blood vessel regeneration. Unfortunately, the long-term degradation and tissue regeneration are normally not presented in these studies. Additionally, most of the works describing drug eluting vascular grafts are focused on the use of techniques that cannot be used for manufacturing of medical devices at an industrial scale. Nonetheless, the use of electrospinning and 3D-printing at the point-of-care is progressing quickly as regulators are provided more guidance [115,116]. Despite all these aspects, there is a clear interest in this area of research as the global vascular graft market is expected to reach eight billion USD by 2030, highlighting that it is an exciting, growing market [117]. Therefore, scientists and private companies are currently working to create a new generation of vascular grafts.

4. Cardiac patches

Cardiac patches are the third type of implantable devices used to treat CVD. They are aimed to repair damaged cardiomyocytes (CMs). Damaged CMs in the ischemic area as a result of heart diseases such as coronary artery disease or myocardial infarction are replaced by fibrotic scar tissue, since these cells (CMs) display poor regenerative ability. Moreover, this scenario correlates with dysfunction of the heart and eventually heart failure due to the loss of its contractile capacity. In this regard, cardiac patches consisting of bioactive compounds and substrate scaffolds, and are considered one of the most valuable therapeutic methods for heart regeneration [36].

Cardiac patches are different than DES or vascular grafts in nature. They are flat devices rather than tubular implants, and they are commonly loaded with cells or other therapeutic compounds (normally biomolecules). This review will focus on cardiac patches intended for sustained delivery of molecules rather than cellular therapy. This is an emerging area of research and there are not many studies describing the use of these devices. Moreover, most of the studies are focused mainly on manufacturing and testing these devices in vitro or using in vivo animal studies.

Cardiac patches are usually composed of a substrate scaffold, which should mimic the features of healthy native myocardium, and a therapeutic ingredient that can be cells or bioactive molecules such as microRNA, growth factors (Hepatocyte growth factor (HGF) or VEGF) and extracellular vesicles like exosomes (Figure 7). Materials used for the manufacture of substrate scaffolds need to meet the following requirements: i) support biological activity, ii) similar mechanical properties of the host tissue and iii) prevent adverse host immune response [119]. In this regard, polymeric scaffolds (natural or synthetic) could offer a wide range of mechanical properties, excellent biocompatibility, and their degradation

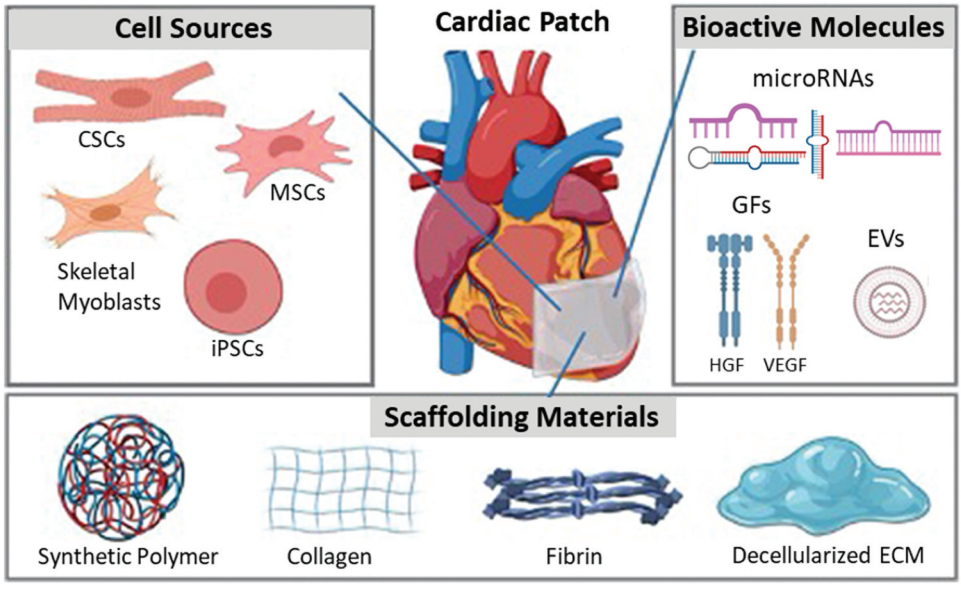

Figure 7. Scaffolding materials and therapeutic ingredients (cells and bioactive molecules) commonly used in the development of cardiac patches. Reproduced with permission from Mei et al. [36] and Singh et al. [118].

rate can be easily manipulated [120]. Cardiac patches represent a more effective therapeutic technology alternative for the treatment of diseased heart tissue, since other therapeutic approaches such as the injection of growth factors or stem cells [121] suffer from low stability and short half-lifetime [120].

Growth factors, extracellular vesicles, and microRNAs are some examples of bioactive molecules loaded in these acellular cardiac patches. Growth factors are naturally occurring bioactive molecules that affect the growth of cells, for example, stimulating cell proliferation or cellular differentiation [122]. For instance, a combination of both growth factors, basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) were loaded in fibrous scaffolds made from poly(l-lactide-co-caprolactone) (PLCL) and poly(2-ethyl-2-oxazoline) (PEOz) by using electrospinning [123]. The results of this study indicated that cells were able to respond at a molecular level by using the growth factors-loaded scaffolds, which also helped to reduce scar tissue formation [123]. In a different work, the authors manufactured a cardiac patch comprising an electronic mesh including multiple electrodes for different purposes, such as cell and tissue electrical stimulation in combination with the sustained release of bioactive molecules within the cardiac tissue [124]. In this study, stromal cell-derived factor-1 (SDF-1) was released from the performed cardiac patch, which was able to stimulate *in vitro* cell migration. Furthermore, the release of SDF-1 could promote better vascularization [124].

Extracellular vesicles are lipid bound small vesicles with a diameter between 30 and 150 nm, which are usually divided into three different categories, exosomes, microvesicles, and apoptotic bodies. These vesicles are secreted by cells into the extracellular space and may play an important role in cell signaling and regulating various intercellular activities [125]. Therefore, extracellular vesicle-loaded cardiac patches have been proposed as a valuable alternative to treat heart diseases. For instance, Liu *et al*. manufactured extracellular vesicle-loaded hydrogels fabricated into cardiac patches in order to avoid the low stability and short half-lifetime of these extracellular vesicles secreted by injected therapeutic cells [126]. In this work, extracellular vesicles were obtained form from cardiomyocytes (CMs) derived from induced pluripotent stem cells. The results showed that the arrhythmic burden, as well as the cardiomyocytes apoptosis rates 24 h after infarction, was reduced, and the ejection-fraction recovery was promoted after implantation of these cardiac patches onto infarcted rat hearts [126]. In a different work, Hamada *et al*. developed extracellular vesicle-loaded cardiac patches made from photocurable adhesive polymer, poly(glycerol-co-sebacate) acrylate ethylene glycol (PGSA-g-EG) for the same purpose of improving the therapeutic value of cell therapy [127]. The outcomes of this study showed that the developed platform was able to release bioactive EVs for a period of 14 days [127].

miRNAs are a class of small single-stranded non-coding RNA molecules involved in the regulation of gene expression. Indeed, it has been shown that some miRNAs can be involved in the cardiovascular repair of the ischemic heart [128]. Despite the significant potential of this therapy, the delivery of these small molecules is still an essential factor for achieving a greater therapy success [129]. Thus, to improve the delivery and stability of these molecules different approaches have been evaluated. For instance, Li *et al*. developed a new miRNAs-containing 3D fibrin-based hydrogel platform containing miRNAs, which significantly enhanced the reprogramming of cardiac fibroblasts into functional CMs [130]. In a different work, Gabisonia *et al*. were able to deliver the human miRNA-199a by using an adeno-associated viral vector platform [131]. The outcomes of this study exhibited that infarcted pigs showed clear improvements in the contractile capacity of their hearts. Moreover, the muscle mass was increased, and scar size was reduced [131]. These results are in line with the de-differentiation and proliferation of CMs, thus suggesting the success of the used miRNAs therapy.

Cardiac patches have the potential to regenerate damaged CMs. As mentioned before, this area of research has attracted recent attention but is currently focused on cell therapy rather than on the delivery of active compounds. These types of devices are normally described in the literature as a proof of concept and their use is normally limited to animal experiments. The results described in the literature are promising. These implants, however, present several challenges before they can be applied into patients. The first limitation is the implantation process. Major surgery is required to implant cardiac patches. Researchers are, however, currently working on addressing this issue. Cardiac patches that can be implanted using minimally invasive procedures have been developed [132]. Nevertheless, this technology is not applicable to every type of patch. Finally, it is important to note that cardiac patches are normally loaded with biomolecules and this is an important factor to consider when considering device manufacturing at industrial scale. Biomolecules are not compatible with some of the techniques used for the manufacturing of medical devices that require high temperatures.

5. Expert opinion

Considering the global burden of cardiovascular disease, there is a clear need for new therapies that reduce mortality whilst maintaining quality of life. Drug eluting devices can provide unattended sustained delivery at the site of implantation. These devices have been used successfully for long-acting systemic delivery of a wide range of drugs for the treatment of chronic conditions such as schizophrenia and HIV. This technology has been applied to implants for the treatment of cardiovascular disease. This review covers the three main types of drug eluting implantable devices described in the literature. Drug eluting stents have been extensively described in the literature and are clinically available. This review describes multiple examples of the use of DES, including key outcomes from clinical trials. These studies suggest that these devices are an effective way to prevent restenosis. New generations of biodegradable stents have promised better outcomes for long-term restenosis. Biodegradable polymers such as poly(lactic acid) or poly(lactic-co-glycolic acid) have been used to prepare drug-loaded stents. This type of devices will

deliver their cargo and degrade after that, preventing potential long-term injuries or inflammation leading to restenosis. However, despite their promising properties, clinical trials showed mixed results. It is important to note that the use of polymeric materials can simplify stent manufacturing as conventional injection molding/extrusion technologies can be used in the manufacturing of the resulting devices. This is in direct comparison to the complexity associated with complex machining or laser cutting technologies required to prepare metal stents. Moreover, the advent of 3D-printing opens the possibility of preparing customized stents. The future looks promising for this area of research. However, new materials and methodologies require regulatory clearance. Currently, regulatory bodies around the world are providing guidance and modifying regulations to prepare the future for 3D-printing at the point of care. In this way, clinicians will be able to prepare customized drug-loaded medical devices for patients. However, this is just the future, and multiple regulatory questions should be addressed before this can be applied. One of the critical aspects is the quality control of 3D-printed devices. Additionally, all these new types of systems will need to be tested in clinical trials to guarantee safety and efficacy.

In addition to DES, this review details current developments in the field of drug eluting vascular grafts and cardiac patches. These devices are commercially available but not yet as drug loaded options. Drug eluting vascular grafts have been extensively discussed in the literature but purely for research purposes only. Researchers working in this area evaluate different materials and manufacturing techniques (mainly electrospinning and 3D-printing) to prepare this type of device. These studies are mainly limited to *in vitro* studies and, in some cases, to *in vivo* animal models. However, the use of drug-eluting vascular grafts has not yet been reported in clinical trials. The lack of interest could potentially be due to the efficacy of autologous transplant of vascular grafts for bypass surgery. This practice is the gold standard for by-pass surgery and only in special cases patients require the use of synthetic vascular grafts. Additionally, the type of drugs used in vascular grafts is mainly limited to anticoagulants/antiplatelet agents and antimicrobial compounds to prevent infection. There is an emerging trend in this area of research exploring the use of 3D-printing for the development of vascular grafts. As mentioned before, this technology allows the development of patient-specific vascular grafts. What has been described for 3D-printing of DES can be applied to vascular grafts. It is clear there are opportunities in this area, however, there is still work to be done and many regulatory questions unanswered. In a similar way, electrospinning has been demonstrated to be a promising alternative to prepare drug-eluting vascular grafts. Electrospun grafts present completely different surface properties than commercially available vascular grafts or 3D-printed vascular grafts. The highly specific surface textures created as a result of the presence of nano-fibers can be used to allow faster drug release and to enhance cell attachment and proliferation. Although literature reports are encouraging, currently, electrospinning is not an industrially viable technique for graft manufacturing and has not been demonstrated to be as versatile as 3D-printing in producing vascular grafts at the point of care.

Cardiac patches have been described as an effective way to provide cardiac regeneration in the treatment of heart disease. This is especially important because ischemic heart disease is the leading cause of death and disability globally. This is especially important considering the limited regeneration capability of cardiomyocytes. These patches can be used to stimulate cardiac tissue regeneration. The majority of the work in this area is focused on cell-laden cardiac patches for regenerative medicine. This review is focused on drug-eluting devices, and therefore cardiac patches loaded with active molecules have been described. Most of these patches are loaded with bioactive molecules such as growth factors, extracellular vesicles, or microRNAs. The stability of these bioactive cargos is limited, as opposed to the small therapeutic molecules used for DES and vascular grafts. Additionally, manufacturing could be challenging as the structure of these devices requires the assembly of many layers and incorporates the complexities associated with biologics. These devices have the potential to revolutionize heart disease treatment, but there are still many aspects to be addressed. Implantation of this type of devices often requires risky and invasive open-chest surgery. However, multiple advances are being developed in this area to develop surgical procedures allowing the implantation of this type of devices in a minimally invasive way.

Funding

J. Domínguez Robles acknowledges financial support from the Ramón y Cajal grant RYC-2021-034357-I funded by MCIN/AEI/10.13039/501100011033 and by the "European Union NextGenerationEU/PRTR".

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

Aaron J. Courtenay http://orcid.org/0000-0002-2651-7839
Ryan F. Donnelly http://orcid.org/0000-0002-0766-4147
Juan Domínguez-Robles http://orcid.org/0000-0002-8654-8434
Eneko Larrañeta http://orcid.org/0000-0003-3710-0438

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors. J Am Coll Cardiol. 2019;74:2529–2532.
2. Vallières K, Laterreur V, Tondreau MY, et al. Human adipose-derived stromal cells for the production of completely autologous self-assembled tissue-engineered vascular substitutes. Acta Biomater. 2015;24:209–219.

3. WHO. Cardiovascular diseases (CVDs). 2017. Available from: https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). [accessed Oct 30, 2019].
4. Fowkes FGR, Aboyans V, Fowkes FJI, et al. Peripheral artery disease: epidemiology and global perspectives. Nat Rev Cardiol. 2017;14:156–170.
5. Grenon SM, Vittinghoff E, Owens CD, et al. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the heart and soul study. Vascular Medicine. 2013;18:176–184.
6. Insull W. The pathology of atherosclerosis: plaque development and plaque responses to medical treatment. Am j med. 2009;122: S3–14.
7. Krishna S, Moxon J, Golledge J. A review of the pathophysiology and potential biomarkers for peripheral artery disease. Int J Mol Sci. 2015;16:11294–11322.
8. McGill HC, McMahan CA, Gidding SS. Preventing heart disease in the 21st century. Circulation. 2008;117:1216–1227.
9. Ng JCK, Toong DWY, Ow V, et al. Progress in drug-delivery systems in cardiovascular applications: stents, balloons and nanoencapsulation. Nanomedicine. 2022;17:325–347.
10. Pipinos II, Judge AR, Selsby JT, et al. The myopathy of peripheral arterial occlusive disease: part 1. functional and histomorphological changes and evidence for mitochondrial dysfunction. Vasc Endovascular Surg. 2008;41:481–489.
11. Simard T, Hibbert B, Ramirez FD, et al. The evolution of coronary stents: a brief review. Can J Cardiol. 2014;30:35–45.
12. Howard-Alpe GM, de Bono J, Hudsmith L, et al. Coronary artery stents and non-cardiac surgery. Br J Anaesth. 2007;98:560–574.
13. Grech ED. Percutaneous coronary intervention I: history and development history of myocardial revascularisation developments in percutaneous intervention. Br Med J. 2003;326:1080–1082.
14. Canfield J, Totary-Jain H. 40 years of percutaneous coronary intervention: history and future directions. J Pers Med. 2018;8:33.
15. Iqbal J, Gunn J, Serruys PW. Coronary stents: historical development, current status and future directions. Br Med Bull. 2013;106:193–211.
16. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med. 1994;331:489–495.
17. George CJ, Baim DS, Brinker JA, et al. One-year follow-up of the Stent Restenosis (STRESS I) study 11 this study was supported in part by Johnson & Johnson interventional systems (cordis), incorporated, Warren, New Jersey. Am J Cardiol. 1998;81:860–865.
18. Hehrlein C. Drug-coated balloons-the importance of packing and dosing antiproliferative drugs. Catheterization Cardiovasc Interventions. 2015;86:287–288.
19. Park S, Kim J, Lee M-K, et al. Fabrication of strong, bioactive vascular grafts with PCL/collagen and PCL/silica bilayers for small-diameter vascular applications. Mater Des. 2019;181:108079.
20. Wang T, Dong N, Yan H, et al. Regeneration of a neoartery through a completely autologous acellular conduit in a minipig model: a pilot study. J Transl Med. 2019;17:24.
21. Jin D, Wu S, Kuang H, et al. Preliminary application of a cell-free mono-layered vascular scaffold in a rabbit model. Mater Des. 2021;198:109301.
22. Mallis P, Kostakis A, Stavropoulos-Giokas C, et al. Future perspectives in small-diameter vascular graft engineering. Bioengineering. 2020;7:160.
23. Zhang F, Xie Y, Celik H, et al. Engineering small-caliber vascular grafts from collagen filaments and nanofibers with comparable mechanical properties to native vessels. Biofabrication. 2019;11:035020.
24. Ravi S, Chaikof EL. Biomaterials for vascular tissue engineering. Regenerative Med. 2010;5:107–120.
25. Chen D, Zhang L, Zhang W, et al. Shapeable large-pore electrospun polycaprolactam cotton facilitates the rapid formation of a functional tissue engineered vascular graft. Mater Des. 2020;191:108631.
26. Kakisis JD, Liapis CD, Breuer C, et al. Artificial blood vessel: the holy grail of peripheral vascular surgery. J Vasc Surg. 2005;41:349–354.
27. Cafarelli A, Losi P, Salgarella AR, et al. Small-caliber vascular grafts based on a piezoelectric nanocomposite elastomer: mechanical properties and biocompatibility. J Mech Behav Biomed Mater. 2019;97:138–148.
28. Cui H, Miao S, Esworthy T, et al. 3D bioprinting for cardiovascular regeneration and pharmacology. Adv Drug Deliv Rev. 2018;132:252–269.
29. Obiweluozor FO, Emechebe GA, Kim D-W, et al. Considerations in the development of small-diameter vascular graft as an alternative for bypass and reconstructive surgeries: a review. Cardiovasc Eng Technol. 2020;11:495–521.
30. Punnakitikashem P, Truong D, Menon JU, et al. Electrospun biodegradable elastic polyurethane scaffolds with dipyridamole release for small diameter vascular grafts. Acta Biomater. 2014;10:4618–4628.
31. Rychter M, Baranowska-Korczyc A, Milanowski B, et al. Cilostazol-loaded poly(ε-caprolactone) electrospun drug delivery system for cardiovascular applications. Pharm Res. 2018;35:32.
32. Domínguez-Robles J, Utomo E, Cornelius VA, et al. TPU-based antiplatelet cardiovascular prostheses prepared using fused deposition modelling. Mater Des. 2022;220:110837. doi: 10.1016/j.matdes.2022.110837.
    - **Production of biodegradable small-diameter vascular grafts with mechanical properties similar to native blood vessels and also prevention of thrombus formation has the potential to be available for the patient in need.**
33. Kim D, Chung JJ, Jung Y, et al. The effect of substance p/heparin conjugated plcl polymer coating of bioinert ePTFE vascular grafts on the recruitment of both ECs and SMCs for accelerated regeneration. Sci Rep. 2019;9:17083.
34. Domínguez-Robles J, Diaz-Gomez L, Utomo E, et al. Use of 3D printing for the development of biodegradable antiplatelet materials for cardiovascular applications. Pharmaceuticals. 2021;14:921.
35. Domínguez-Robles J, Shen T, Cornelius VA, et al. Development of drug loaded cardiovascular prosthesis for thrombosis prevention using 3D printing. Mater Sci Eng C. 2021;129:112375.
36. Mei X, Cheng K. Recent development in therapeutic cardiac patches. Front Cardiovasc Med. 2020;7. DOI:10.3389/fcvm.2020.610364.
37. Bowen PK, Shearier ER, Zhao S, et al. Biodegradable metals for cardiovascular stents: from clinical concerns to recent Zn-alloys. Adv Healthc Mater. 2016;5:1121–1140.
38. Buccheri D, Piraino D, Andolina G, et al. Understanding and managing in-stent restenosis: a review of clinical data, from pathogenesis to treatment. J Thorac Dis. 2016;8:E1150–1162.
39. Wang L, Wang H, Dong P, et al. Long-term outcomes of drug-eluting versus bare-metal stent for ST-elevation myocardial infarction. Arq Bras Cardiol. 2014. DOI:10.5935/abc.20140070
40. Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents. JACC: Cardiovasc Interv. 2013;6:1267–1274.
41. Colombo A, Giannini F, Briguori C. Should we still have bare-metal stents available in our catheterization laboratory? J Am Coll Cardiol. 2017;70:607–619.
42. Inoue T, Croce K, Morooka T, et al. Vascular inflammation and repair. JACC: Cardiovasc Interv. 2011;4:1057–1066.
43. Cornelissen A, Vogt FJ. The effects of stenting on coronary endothelium from a molecular biological view: time for improvement? J Cell Mol Med. 2019;23:39–46.
44. Livingston M, Tan A. Coating techniques and release kinetics of drug-eluting stents. J Med Device. 2016;10. DOI:10.1115/1.4031718.
45. Hassan S, Ali MN, Ghafoor B. Evolutionary perspective of drug eluting stents: from thick polymer to polymer free approach. J Cardiothorac Surg. 2022;17:65.
46. Borhani S, Hassanajili S, Ahmadi Tafti SH, et al. Cardiovascular stents: overview, evolution, and next generation. Prog Biomater. 2018;7:175–205.

47. Kukreja N, Onuma Y, Daemen J, et al. The future of drug-eluting stents. Pharmacol Res. 2008;57:171–180.
48. Papafaklis MI, Chatzizisis YS, Naka KK, et al. Drug-eluting stent restenosis: effect of drug type, release kinetics, hemodynamics and coating strategy. Pharmacol Ther. 2012;134:43–53.
49. Waksman R. A new generation of drug-eluting stents: indications and outcomes of bioresorbable vascular scaffolds. Cleve Clin J Med. 2017;84:e20–24.
50. Whitbeck MG, Applegate RJ. Second generation drug-eluting stents: a review of the everolimus-eluting platform. Clin Med Insights Cardiol. 2013;7:CMC.S11516.
51. Katz G, Harchandani B, Shah B. Drug-eluting stents: the past, present, and future. Curr Atheroscler Rep. 2015;17:11.
52. Koskinas KC, Chatzizisis YS, Antoniadis AP, et al. Role of endothelial shear stress in stent restenosis and thrombosis. J Am Coll Cardiol. 2012;59:1337–1349.
53. Pandya B. Biodegradable polymer stents *vs* second generation drug eluting stents: a meta-analysis and systematic review of randomized controlled trials. World J Cardiol. 2016;8:240.
54. Kalra A, Rehman H, Khera S, et al. New-generation coronary stents: current data and future directions. Curr Atheroscler Rep. 2017;19:14.
55. Lee PH, Kwon O, Ahn J-M, et al. Safety and effectiveness of second-generation drug-eluting stents in patients with left main coronary artery disease. J Am Coll Cardiol. 2018;71:832–841.
56. Onuma Y, Miquel-Hebert K, Serruys PW. Five-year long-term clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery disease: the SPIRIT II trial, EuroIntervention. EuroIntervention. 2013;8:1047–1051.
57. Gada H, Kirtane AJ, Newman W, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents. JACC: Cardiovasc Interv. 2013;6:1263–1266.
58. Stone GW, Rizvi A, Sudhir K, et al. Randomized comparison of everolimus- and paclitaxel-eluting stents. J Am Coll Cardiol. 2011;58:19–25.
59. Iqbal J, Serruys PW, Silber S, et al. Comparison of zotarolimus- and everolimus-eluting coronary stents. Circ Cardiovasc Interv. 2015;8. doi: 10.1161/CIRCINTERVENTIONS.114.002230.
•• **Clinical trial showing that patients treated with 1st generation DES showed similar outcomes than patients treated with 2nd generation DES 5 years post implantation.**
60. El-Hayek G, Bangalore S, Casso Dominguez A, et al. Meta-analysis of randomized clinical trials comparing biodegradable polymer drug-eluting stent to second-generation durable polymer drug-eluting stents. JACC: Cardiovasc Interv. 2017;10:462–473.
61. Hou D, Huibregtse B, Dawkins K, et al. Current State of Bioabsorbable Polymer-Coated Drug-Eluting Stents. Curr Cardiol Rev. 2017;13(2). DOI: https://doi.org/10.2174/1573403X12666161222155230
62. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J. 2012;33:1214–1222.
63. Chisari A, Pistritto A, Piccolo R, et al. The ultimaster biodegradable-polymer sirolimus-eluting stent: an updated review of clinical evidence. Int J Mol Sci. 2016;17:1490.
64. Michell, Technologies. MiStent. 2020. Available from: http://www.micell.com/products/. [cited Feb 28, 2020].
65. MicroPort. MicroPort® receives CE mark for Firehawk Liberty™, a new generation rapamycin target eluting coronary stent system. 2019. Available from: http://www.microport.com/news-detail-2082. [cited Feb 28, 2020].
66. Seth A. Moving Towards biomimicry – the development of the novel BioMime™ Sirolimus-eluting coronary stent system. Eur Cardionlog Rev. 2010;6:78–82.
67. Commission E. CE marking. 2020. Available from: https://ec.europa.eu/growth/single-market/ce-marking_en. [cited Mar 17, 2020].
68. Muramatsu T, Onuma Y, Zhang Y-J, et al. Progress in treatment by percutaneous coronary intervention: the stent of the future. Revista Española de Cardiología. 2013;66:483–496. Engilsh. doi: 10.1016/j.recesp.2012.12.009
69. Kereiakes DJ, Windecker S, Jobe RL, et al. Clinical outcomes following implantation of thin-strut, bioabsorbable polymer-coated, everolimus-eluting SYNERGY stents. Circ Cardiovasc Interv. 2019;12. DOI:10.1161/CIRCINTERVENTIONS.119.008152.
70. FDA, SYNERGY™ everolimus-eluting platinum chromium coronary stent system: patient information guide. n.d. Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150003d.pdf. [cited Feb 20, 2020].
71. Meredith IT, Verheye S, Dubois CL, et al. Primary endpoint results of the EVOLVE trial. J Am Coll Cardiol. 2012;59:1362–1370.
72. Meredith IT, Verheye S, Dubois C, et al. Final five-year clinical outcomes in the EVOLVE trial: a randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. EuroIntervention. 2018;13:2047–2050.
73. Forrestal BJ, Case BC, Yerasi C, et al. The orsiro ultrathin, bioresorbable-polymer sirolimus-eluting stent: a review of current evidence. Cardiovasc Revascularization Med. 2020;21:540–548. doi: 10.1016/j.carrev.2019.12.039.
•• **Clinical trial showing that patients treated with 3rd generation DES showed lower target vessel failure and target lesion failure rates than patients treated with 2nd generation DES.**
74. Saito S, Toelg R, Witzenbichler B, et al. BIOFLOW-IV, a randomised, intercontinental, multicentre study to assess the safety and effectiveness of the Orsiro sirolimus-eluting stent in the treatment of subjects with de novo coronary artery lesions: primary outcome target vessel failure at 12 months. EuroIntervention. 2019;15:e1006–1013.
75. Lefèvre T, Haude M, Neumann F-J, et al. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent. JACC: Cardiovasc Interv. 2018;11:995–1002.
76. Huang Y, Ng HCA, Ng XW, et al. Drug-eluting biostable and erodible stents. JControlled Release. 2014;193:188–201.
77. Thipparaboina R, Khan W, Domb AJ. Eluting combination drugs from stents. Int J Pharm. 2013;454:4–10.
78. Lee CW, Park D-W, Seung KB, et al. Comparison of dual drug-eluting cilotax stent and paclitaxel-eluting taxus liberte stent in native coronary artery lesions. Am J Cardiol. 2011;107:990–994.
79. Adriaenssens T, Mehilli J, Wessely R, et al. Does addition of estradiol improve the efficacy of a rapamycin-eluting stent? J Am Coll Cardiol. 2007;49:1265–1271.
80. OrbusNeich. Combo duel therapy stent. 2020. Available from: https://www.orbusneich.com/en/products/dual-therapy-stent/combo. [cited Mar 4, 2020].
81. Chandrasekhar J, Martin K, Mehran R. Role of coronary drug-eluting stents in current clinical practice. Clinic Pharmacist. 2016;8:11. DOI:10.1211/PJ.2016.20201885.
82. Jakobsen L, Christiansen EH, Freeman P, et al. Randomized clinical comparison of the dual-therapy CD34 antibody-covered sirolimus-eluting combo stent with the sirolimus-eluting orsiro stent in patients treated with percutaneous coronary intervention: the SORT OUT X trial. Circulation. 2021;143:2155–2165.
83. Wang R, Lu J, Yin J, et al. A TEMPOL and rapamycin loaded nanofiber-covered stent favors endothelialization and mitigates neointimal hyperplasia and local inflammation. Bioact Mater. 2023;19:666–677.
84. Zhang B, Qin Y, Yang L, et al. A polyphenol-network-mediated coating modulates inflammation and vascular healing on vascular stents. ACS Nano. 2022;16:6585–6597.
85. Hu T, Lin S, Du R, et al. Design, preparation and performance of a novel drug-eluting stent with multiple layer coatings. Biomater Sci. 2017;5:1845–1857.
86. Cheng Y, Zhang X, Liu R, et al. Bioinspired vascular stents with microfluidic electrospun multilayer coatings for preventing in-stent restenosis. Adv Healthc Mater. 2022;11:2200965.
87. Gareri C, de Rosa S, Indolfi C. MicroRNAs for restenosis and thrombosis after vascular injury. Circ Res. 2016;118:1170–1184.

88. Santulli G, Wronska A, Uryu K, et al. A selective microRNA-based strategy inhibits restenosis while preserving endothelial function. J Clin Investig. 2014;124:4102–4114.
89. Jiang W, Zhao W, Zhou T, et al. A review on manufacturing and post-processing technology of vascular stents. Micromachines (Basel). 2022;13:140.
90. Galyfos G, Geropapas G, Stefanidis I, et al. Bioabsorbable stenting in peripheral artery disease. Cardiovasc Revascularization Med. 2015;16:480–483.
91. Nilsson H. Vasomotion: mechanisms and physiological importance. Mol Interv. 2003;3:79–89.
92. Colombo A, Azzalini L. Bioresorbable Scaffolds. JACC: Cardiovasc Interv. 2017;10:2360–2362.
93. Regazzoli D, Leone PP, Colombo A, et al. New generation bioresorbable scaffold technologies: an update on novel devices and clinical results. J Thorac Dis. 2017;9:S979–985.
94. Omar WA, Kumbhani DJ. The current literature on bioabsorbable stents: a review. Curr Atheroscler Rep. 2019;21:54.
95. Sotomi Y, Onuma Y, Collet C, et al. Bioresorbable Scaffold. Circ Res. 2017;120:1341–1352.
96. Abizaid A, Carrié D, Frey N, et al. 6-month clinical and angiographic outcomes of a novel radiopaque sirolimus-eluting bioresorbable vascular scaffold. JACC: Cardiovasc Interv. 2017;10:1832–1838.
97. ARTDIVA study: first in man safety evaluation of the ART18Z bioresorbable stent. n.d. Available from: https://clinicaltrials.gov/ct2/show/study/NCT01761578. [cited Nov 22, 2019].
98. Mattesini A, Bartolini S, Dini CS, et al. The DESolve novolimus bioresorbable Scaffold: from bench to bedside. J Thorac Dis. 2017;9:S950–958.
99. Abizaid A, Costa RA, Schofer J, et al. Serial multimodality imaging and 2-year clinical outcomes of the novel DESolve novolimus-eluting bioresorbable coronary scaffold system for the treatment of single de novo coronary lesions. JACC: Cardiovasc Interv. 2016;9:565–574.
100. Rapetto C, Leoncini M. Magmaris: a new generation metallic sirolimus-eluting fully bioresorbable scaffold: present status and future perspectives. J Thorac Dis. 2017;9:S903–913.
101. Haude M, Ince H, Abizaid A, et al. Safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de-novo coronary artery lesions (BIOSOLVE-II): 6 month results of a prospective, multicentre, non-randomised, first-in-man trial. Lancet. 2016;387:31–39.
102. Panaich S, Schreiber T, Grines C. Bioresorbable Scaffolds. Interventional Cardiol Rev. 2014;9:175. doi: 10.15420/icr.2014.9.3.175.
•• **Review article presenting findings about performance of biodegradable DES vs. conventional coated DES.**
103. Sánchez PF, Brey EM, Briceño JC. Endothelialization mechanisms in vascular grafts. J Tissue Eng Regen Med. 2018;12:2164–2178.
104. Dahl SLM, Kypson AP, Lawson JH, et al. Readily available tissue-engineered vascular grafts. Sci Transl Med. 2011;3. DOI:10.1126/scitranslmed.3001426.
105. Singh C, Wong C, Wang X. Medical textiles as vascular implants and their success to mimic natural arteries. J Funct Biomater. 2015;6:500–525.
106. Sayers RD, Raptis S, Berce M, et al. Long-term results of femorotibial bypass with vein or polytetrafluoroethylene. Br J Surg. 2003;85:934–938.
107. Spadaccio C, Nappi F, de Marco F, et al. Preliminary in vivo evaluation of a hybrid armored vascular graft combining electrospinning and additive manufacturing techniques. Drug Target Insights. 2016;10(s1):DTI.S35202.
108. Dzenis Y. Spinning continuous fibers for nanotechnology. Science. 2004;304:1917–1919. DOI:10.1126/science.1099074. 1979.
109. Norouzi SK, Shamloo A. Bilayered heparinized vascular graft fabricated by combining electrospinning and freeze drying methods. Mater Sci Eng C. 2019;94:1067–1076.
110. Hu Y-T, Pan X-D, Zheng J, et al. In vitro and in vivo evaluation of a small-caliber coaxial electrospun vascular graft loaded with heparin and VEGF. Int J Surg. 2017;44:244–249.
111. Shitole AA, Giram PS, Raut PW, et al. Clopidogrel eluting electrospun polyurethane/polyethylene glycol thromboresistant, hemocompatible nanofibrous scaffolds. J Biomater Appl. 2019;33:1327–1347.
112. Serpelloni S, Peden EK, Taraballi F, et al. Biodegradable drug-eluting nanofiber-loaded vascular graft. J Vasc Surg. 2021;74:e49–50. doi: 10.1016/j.jvs.2021.06.081.
• **The development of a chitosan-based nanofiber coating of vascular prostheses has yielded encouraging results from preclinical testing, laying a solid scientific groundwork for future clinical studies.**
113. Melchiorri AJ, Hibino N, Best CA, et al. 3D-Printed biodegradable polymeric vascular grafts. Adv Healthc Mater. 2016;5:319–325.
114. Jia W, Gungor-Ozkerim PS, Zhang YS, et al. Direct 3D bioprinting of perfusable vascular constructs using a blend bioink. Biomaterials. 2016;106:58–68. doi: 10.1016/j.biomaterials.2016.07.038.
•• **An innovative combination and flexible 3D bioprinting approach for direct deposition of the cell-laden permeable vascular construct has been explored. Viable and functional vessels imitating early development of the native blood vessels may be formed as a result of the encapsulation of the associated vascular cell types.**
115. Stoddard RJ, Steger AL, Blakney AK, et al. In pursuit of functional electrospun materials for clinical applications in humans. Ther Deliv. 2016;7:387–409.
116. Beitler BG, Abraham PF, Glennon AR, et al. Interpretation of regulatory factors for 3D printing at hospitals and medical centers, or at the point of care. 3D Print Med. 2022;8:7.
117. Smita N, Prathmesh B, Onkar S. Vascular grafts market; global opportunity analysis and industrial forecast. Allied Market Research. 2022p. 1–7. Available from: https://www.alliedmarketresearch.com/vascular-graft-market. [citedd Nov 27, 2022].
118. Singh G, Storey KB. MicroRNA cues from nature: a roadmap to decipher and combat challenges in human health and disease? Cells. 2021;10:3374.
119. Jawad H, Ali NN, Lyon AR, et al. Myocardial tissue engineering: a review. J Tissue Eng Regen Med. 2007;1:327–342.
120. McMahan S, Taylor A, Copeland KM, et al. Current advances in biodegradable synthetic polymer based cardiac patches. J Biomed Mater Res A. 2020;108:972–983.
121. Qiao L, Hu S, Liu S, et al. MicroRNA-21-5p dysregulation in exosomes derived from heart failure patients impairs regenerative potential. J Clin Investig. 2019;129:2237–2250.
122. Sharma D, Jaggi AS, Bali A. Clinical evidence and mechanisms of growth factors in idiopathic and diabetes-induced carpal tunnel syndrome. Eur J Pharmacol. 2018;837:156–163.
123. Lakshmanan R, Kumaraswamy P, Krishnan UM, et al. Engineering a growth factor embedded nanofiber matrix niche to promote vascularization for functional cardiac regeneration. Biomaterials. 2016;97:176–195.
124. Feiner R, Engel L, Fleischer S, et al. Engineered hybrid cardiac patches with multifunctional electronics for online monitoring and regulation of tissue function. Nat Mater. 2016;15:679–685.
125. Raposo G, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. J Cell Biol. 2013;200:373–383.
126. Liu B, Lee BW, Nakanishi K, et al. Cardiac recovery via extended cell-free delivery of extracellular vesicles secreted by cardiomyocytes derived from induced pluripotent stem cells. Nat Biomed Eng. 2018;2:293–303. doi: 10.1038/s41551-018-0229-7.
•• **Researchers were inspired to develop an engineered hydrogel patch by the therapeutic potential of extracellular vesicles (EVs) secreted by therapeutic cells, such as cardiomyocytes (CMs) derived from induced pluripotent stem cells. When implanted onto infarcted rat hearts, the patch reduced the arrhythmic burden and promoted ejection-fraction recovery.**
127. Hamada T, Dubois JLN, Bellamy V, et al. In vitro controlled release of extracellular vesicles for cardiac repair from poly(glycerol sebacate) acrylate-based polymers. Acta Biomater. 2020;115:92–103.
128. Yang H, Qin X, Wang H, et al. An in vivo miRNA delivery system for restoring infarcted myocardium. ACS Nano. 2019;13:9880–9894.

129. Maegdefessel L, Azuma J, Toh R, et al. MicroRNA-21 blocks abdominal aortic aneurysm development and nicotine-augmented expansion. Sci Transl Med. 2012;4. DOI:10.1126/scitranslmed.3003441.
130. Li Y, Dal-Pra S, Mirotsou M, et al. Tissue-engineered 3-dimensional (3D) microenvironment enhances the direct reprogramming of fibroblasts into cardiomyocytes by microRnas. Sci Rep. 2016;6:38815.
131. Gabisonia K, Prosdocimo G, Aquaro GD, et al. MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs. Nature. 2019;569:418–422.
132. Montgomery M, Ahadian S, Davenport Huyer L, et al. Flexible shape-memory scaffold for minimally invasive delivery of functional tissues. Nat Mater. 2017;16:1038–1046.