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Current Opinion in Biomedical Engineering

Intelligent biomaterials for cardiovascular applications

S. S. V. Tetali, A. T. R. Fricker, Y. A. van Domburg and I. Roy

Abstract

Cardiovascular disease remains a leading cause of morbidity and mortality worldwide, and as such, research in cardiovascular medicine is continuously evolving. Recent advances in technology have created opportunities for improving the diagnosis and management of cardiovascular disease. This review article summarizes the use of innovative polymeric biomaterials for various cardiovascular applications, highlighting promising results obtained in the past five years.

The review begins by discussing the use of artificial blood vessels and coronary artery stents with biosensors for coronary artery disease management. Additionally, the studies on cardiac patches for heart failure management are evaluated. The review also covers recent advancements in artificial intelligence and real-time health monitoring for diagnosing cardiovascular conditions such as arrhythmias and structural heart disease. New catheters for epicardial mapping and stretchable conducting polymers for surface electrodes have improved diagnostic capabilities. The review also examines advancements in engineering with intelligent biomaterials for unique and sustainable treatment options. This includes piezoelectric and triboelectric nanogenerators for improved cardiovascular devices, reducing the need for battery changes and the risk of infections.

Overall, the review provides a comprehensive analysis of innovative polymeric biomaterials for various cardiovascular diagnostic and treatment modalities. It summarizes recent studies that demonstrate the potential of these materials for improving patient outcomes and ultimately reducing the burden of cardiovascular disease. As the field of cardiovascular medicine continues to evolve, these advancements may pave the way for further progress in the diagnosis and management of cardiovascular disease.

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Keywords

Cardiovascular, Polyhydroxyalkanoates, Polymers, Bacterial cellulose.

Introduction

Cardiovascular disease (CVD) is a generic term for conditions affecting the heart and blood vessels [1]. These conditions range from coronary artery disease causing angina or myocardial infarctions to cardiomyopathies leading to heart failure, valvular heart disease and arrhythmias [2]. CVD is the leading cause of death worldwide [3]. World Health Organisation statistics show that 32% of all global deaths in 2019 were due to cardiovascular disease with the main proportion of this (85%), due to myocardial infarctions and strokes [4]. This is a significant health burden and more needs to be done to tackle these conditions from diagnosis through to management.

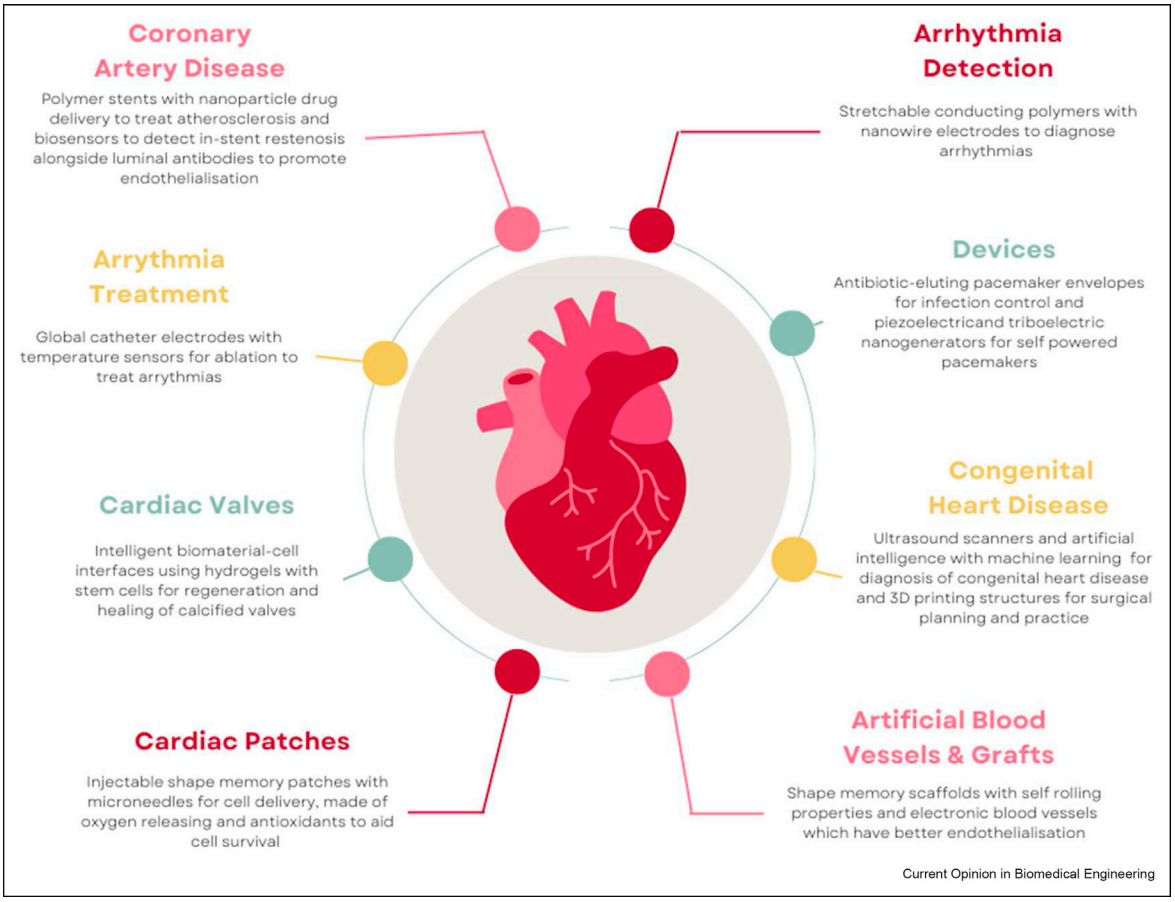
Current clinical practice for significant coronary artery disease is through implantation of drug-eluting metallic stents. In this review, we focus on how these stents could be improved by using polymeric stents instead of metal, that have luminal antibodies and biosensors to detect and reduce in-stent restenosis, whilst using nanoparticle drug delivery systems to treat atherosclerosis. When stents cannot be inserted due to the extent of coronary artery disease, patients may be treated using coronary artery bypass surgery; however, not all patients have suitable blood vessels to be used as grafts. In these circumstances, artificial blood vessels manufactured using shape memory scaffolds with peptides to induce endothelialisation can be utilised. If myocardial infarctions are not treated in time, heart failure can develop, which can be managed using injectable shape memory cardiac patches. These can help heal myocardial damage using microneedles for cell delivery with oxygen releasing antioxidant cardiac patch, made from antioxidant polyurethane with calcium peroxide incorporated as an oxygen generating material [5]. This combination provides a sustained antioxidant behaviour and release of oxygen, whilst inducing vascularisation, regeneration and decrease in oxidative stress, allowing healing of the myocardial tissue [5].

With time, this myocardial damage can lead to scar tissue formation and life-threatening arrhythmias can develop. The development of novel polymers can now aid the diagnosis of these arrhythmias, which have been historically challenging to diagnose due to poor skin electrode interfaces. Additionally, longer monitoring of arrhythmias can now be achieved using stretchable

conducting polymers and nanowire electrodes. Once diagnosed, improvements in electrophysiology electrodes using global catheters with temperature sensing have enhanced the reliability of cardiac electrophysiology mapping. Additionally, precision in ablation has improved, allowing for full isolation of electrical circuits that are leading to cardiac arrhythmias and hence higher success rates in treatment can now be achieved. If full isolation of these life-threatening arrhythmias cannot be achieved, then cardiac devices such as defibrillators can save a patient's life. However, these devices once inserted need changing regularly as the battery needs replacement every 10 years. Progress made in triboelectric and piezoelectric nanogenerators, remove the need for changing these devices for battery replacements, thereby reducing infection risks and the need for repeat procedures [6–8].

Furthermore, cardiovascular diagnostics have been improved with the development of stamp-sized ultrasound scanners using piezoelectric transducers and hydrogels for high-quality acoustic performance [9]. This technology alongside developments in artificial intelligence and machine learning now allows the diagnosis of structural heart disease both in early and late life with extraordinary accuracy. In this review, we show how calcified degenerative valvular disease can be healed using shape memory polymers which can grow with the patient. In addition to this, we discuss how nanocrystalline cellulose hydrogels have been shown to have anti-inflammatory properties which support the regeneration of healthy valvular tissue. Combining this smart hydrogel or other hydrogels with encapsulated microRNAs such as cel-miR-67, miR-141, miR-638 and miR-132 could reduce calcification and improve disease outcome further [10–12].

Figure 1



A summary of a range of cardiovascular applications of intelligent biomaterials over the last 5 years. Amongst these applications, significant work has been carried out on the use of polymeric coronary artery stents with nanoparticle drug delivery targeted directly to the areas of coronary artery disease; cardiac patches using a combination of materials that provide a sustained antioxidant behaviour and release of oxygen, whilst inducing vascularisation, regeneration and decrease in oxidative stress whilst simultaneously being injectable and containing microneedles for cell delivery directly into scarred myocardial tissue; antibiotic-eluting pacemaker envelops for infection control which are now used in clinical practice.

The combination of all these innovations shows great promise for the future of cardiovascular medicine. Fig. 1 summarises some of the common problems within cardiovascular medicine and the proposed solutions using the progress made over the last 5 years.

In recent years, there have been many publications on cardiovascular applications; however, this comprehensive review paper on cardiovascular applications unveils the immense potential and ground-breaking advancements that are revolutionizing the field of cardiology. Through the mentioned research and technological innovations, remarkable progress has been made in diagnostic tools and therapeutic interventions, all aimed at combating the global burden of cardiovascular diseases. This review paper presents a realistic coverage of future potential [13–15]. The current clinical limitations for each cardiac application have been described, along with a description of novel biomaterials that have been used to solve these problems. The first topic covered is the significant progress that has been made in the management of coronary artery disease with advances in coronary artery stent development and artificial blood vessels, followed by the description of advances in heart failure management using cardiac patches. Further, complications of myocardial infarction such as life-threatening arrhythmias have been described including their successful detection with pinpoint accuracy, followed by targeted ablation or the implantation of cardiac devices for the delivery of life-saving treatment. Finally, structural heart disease diagnosis and potential treatment options ranging from congenital abnormalities diagnosed at a foetal stage to degenerative changes with age has been described. Hence, this review addresses the use of novel biomaterials in the last five years and highlights their clinical applications in the context of cardiovascular disease, including further work required in the field.

Coronary artery disease

Coronary artery disease is a systemic low-grade inflammatory process triggered in areas where there is high turbulence in blood flow, usually through hypertension, which damages the endothelium of coronary arteries. This damaged area allows subendothelial accumulation of cholesterol containing lipoproteins, in particular low-density lipoprotein cholesterol. This deposition under the endothelium triggers an inflammatory response and over time a necrotic core can form. This accumulation is known as an atherosclerotic plaque and becomes unstable as it progresses, leading to rupture and consequential platelet activation, triggering clot formation [16,17]. This leads to a myocardial infarction through myocardial tissue necrosis caused by restricted blood supply to the myocardium and in turn this damage to the myocardium can lead to heart failure.

Coronary artery stents

The current gold standard treatment of coronary artery disease is the use of drug-eluting metallic stents in addition to medications. The drug coating on the abluminal surface of the current stents is key to their success, as it can dampen inflammatory responses within the atherosclerotic plaque and reduce progression. However, even though this treatment is effective for atherosclerotic disease management, the shear stresses caused by the stent can induce smooth muscle cell proliferation and cause in-stent restenosis over time [18]. The stents in this study were found to have eluted 80% of the antiproliferative drug from the scaffold within 30 days, which would only be effective for the initial trauma caused to the vessel wall when the stent was initially implanted [18]. Therefore, current research has focused heavily on how to alleviate this problem.

Recent studies have shown that polymeric stents can be used as an alternative to metallic stents both as an alternative scaffold as well as for drug elution [19]. Polyhydroxyalkanoates (PHAs) have shown great promise as polymeric stents as they are biocompatible, nontoxic and most importantly biodegradable and haemocompatible [20]. Puppi et al. have used computer-aided wet spinning to manufacture tubular stents using poly (3-hydroxybutyrate-*co*-3-hydroxyhexanoate), P (3HB-*co*-3HHx), which showed proliferation of human umbilical vein endothelial cells *in vitro*, and low levels of thrombogenicity when in contact with human blood [20]. Though these tubular stents can provide structural support, one of the limitations is that they cannot provide targeted drug elution to the atherosclerotic plaque area. Recent studies have started to focus more on controlled drug delivery in close proximity of the coronary arterial walls to directly treat the atherosclerotic disease combined with deactivation on the luminal side of the stent to reduce the risks of in stent restenosis and thrombosis [18,21]. This deactivation of the luminal side is brought about by the promotion of rapid endothelialisation. This is facilitated by endothelial progenitor cell capturing through anti-human CD34 antibodies attached to the luminal surface of the stent [22].

Further studies have shown that this controlled drug delivery in the form of nanoparticles due to their high surface area to volume ratio can cross the endothelial layer of the coronary artery wall and efficiently deliver the drug to the atherosclerotic plaque underneath [22]. PHA-based nanoparticles/microparticles for drug delivery is a promising field where drugs are easily encapsulated or entrapped inside PHAs and released in a controlled manner due to their porosity and degradation [23]. A recent study has shown that poly (3-hydroxybutyrate-*co*- 4-hydroxybutyrate), P (3HB-*co*-4HB), encapsulating rapamycin as a drug coating on stents has shown excellent results due to its ductility

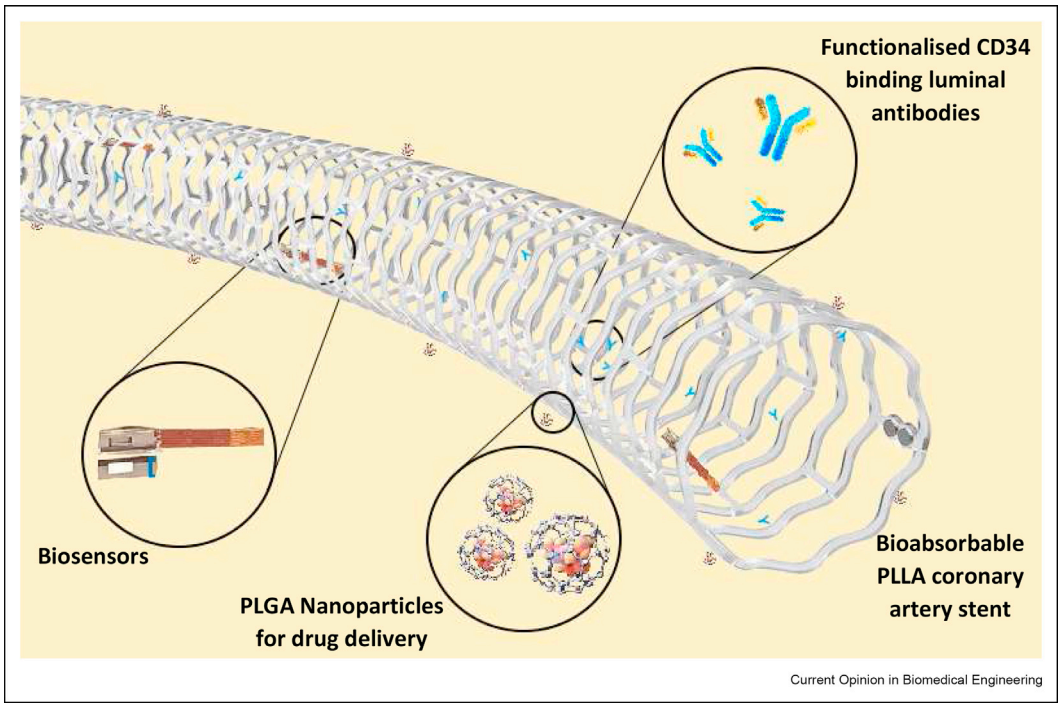
and adhesiveness with excellent biocompatibility and haemocompatibility [24]. Various stimulators such as electric fields, light irradiation and alteration in pH can aid with targeted drug delivery i.e. to the atherosclerotic plaque rather than the endothelium alone [22]. An *in vivo* study using adult male Spraque-Dawley rats using poly(lactide-*co*-glycolide) (PLGA) nanoparticle abluminally coating the cardiovascular stents delivering N-nitrosomelatonin exhibited considerable reduction in platelet aggregation compared to those deployed with the control stents, which exhibited increased neo intima formation showing great promise for targeted therapies [22]. Wang et al. loaded PLGA nanoparticles with paclitaxel and used magnetic nanoparticles-coated microbubbles for the delivery with further stimulation using low intensity focused ultrasound [25]. The study used an *ex-vivo* stented porcine artery model to assess the drug delivery, and they found that the use of low intensity focused ultrasound and an external magnetic field were effective in improving the accumulation and penetration of paclitaxel into the tunica media of the arterial wall improving retention time of paclitaxel release and reducing in stent restenosis. In addition to targeted drug delivery, attention has been drawn to functionalisation of the luminal surface of the stent using CD34-binding antibodies aimed at capturing endothelial progenitor cells to promote re-endothelialisation [22]. In a study conducted on a porcine model, it was found that when anti-CD34 antibody-coated polytetrafluoroethylene grafts were implanted *in vivo*, the coated grafts exhibited early endothelialisation, and by 28 days, 85% of stent struts were coated by ECs in comparison to only 32% of stent endothelialisation of the non-coated grafts [22]. This can have significant clinical impact by reducing the time required for dual antiplatelet therapy [26]. However, one of the limitations of this study is that the anti-CD34+ progenitor cells can differentiate into vascular smooth muscle cells and haematopoietic stem cells, meaning they can potentially cause obstruction and induce intimal hyperplasia if not controlled [22].

Additionally, focus has also switched to biosensors within stents. These biosensors use electrical impedance spectroscopy which passes an alternating current across a set of electrodes and records the impedance. This impedance varies across different tissues aiding with the detection of different cell types. Previously, these electrodes were made of gold and glass, but due to their large size and risk of fracture, they have now been developed using silicone and platinum and are attached to the luminal surface of coronary artery stents [27]. These sensors constantly monitor coronary artery physiology and can detect different cell types associated with in-stent restenosis and are also able to differentiate between atherosclerotic plaque components and blood clots [27]. In this study, the sensors were seeded with primary mouse aortic smooth muscle cells and mouse endothelial cells, and through the difference in impedance, they were able to differentiate between the two cell types. The study also assessed the impedance of both clotted and heparinised blood and was able to differentiate between the two. This is particularly useful for future insight into causes of restenosis as well as aiding preventative medication development; however, one of the limitations of this product is the bulky size and inability to deform, making it difficult to deliver into the coronary arteries [27]. Fig. 2 illustrates how the nanoparticle drug delivery, functionalised antibodies on the luminal layer and biosensors are placed on the surface of the stents to monitor and aid reduction in stent restenosis.

Artificial blood vessels

Another form of treatment for coronary artery disease is coronary artery bypass surgery using the patient's own blood vessel to reroute blood to the heart [17]. However, when there is a problem within coronary arteries, it is likely to be present in other blood vessels too, and sometimes, this can prevent patients from undergoing bypass surgery [17]. This is where artificial blood vessels can be helpful. Bacterial cellulose (BC) has shown great potential as artificial blood vessels due to its biocompatibility and mouldability as it can form tubular structures when moulded in culture media using cylindrical glass and silicone [28]. BC has also shown positive results in *in vivo* studies with the grafts being easily suturable and showing no signs of dilation, inflammation or thrombosis [28]. Shape-memory scaffolds have been a recent focus of blood vessel regenerative medicine research [29]. Materials of this type enable the engineered constructs to be seeded with cells whilst in a flat orientation, meaning that cells can be cultured homogeneously over the surface of the tube. One such study used novel PHA-based polyurethane which displayed shape-memory behaviour upon immersion in water. The presence of telechelic-hydroxylated PHA (PHA-diols) provided thermo-responsive domains in the material, and polyethylene glycol provided water-responsive regions, therefore, producing a water-thermal responsive biomaterial. This material has potential in many biomedical applications, with the triggering of a self-rolling 3D scaffold, providing good mechanical properties including compressibility and stretchability, promising for tissue engineered blood vessels [30]. Whilst this study provides a promising set of results, testing of this shape-memory scaffold *in vitro* is required to show the biocompatibility of the materials used, and then *in vivo* to ensure that the scaffold performs as expected in an animal model. If further testing shows that the scaffold is suitable for use *in vivo*, then the applications could be even wider than for artificial blood vessels. In a study published in the following year by Chen et al. (2020), poly (lactide-glycolide-trimethylene carbonate) was used where it maintained a temporary flat shape at 20 °C and subsequently self-rolled into a tubular shape when incubated at 37 °C [31]. This study carried

Figure 2



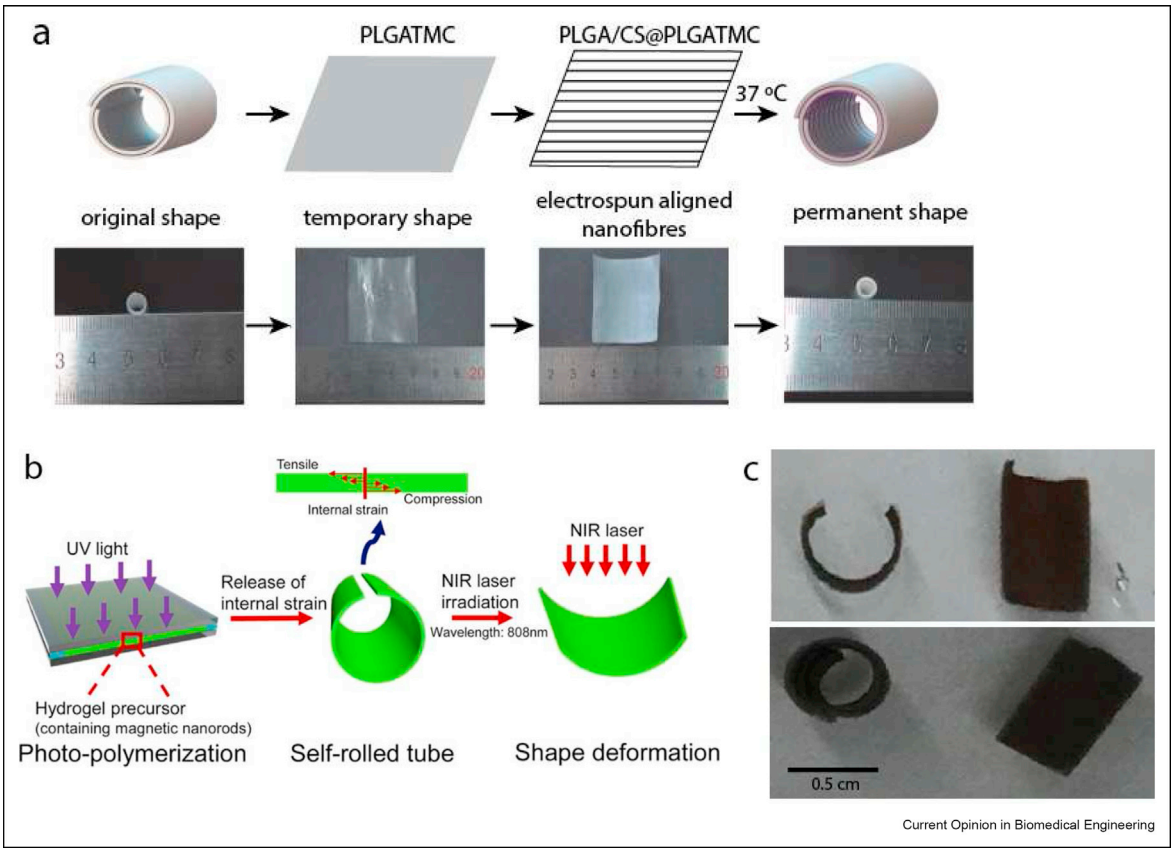
An illustration of a bioabsorbable polymeric stent made using PLLA with platinum and silicon biosensors for sensing in stent restenosis and PLGA nanoparticle drug delivery to treat atherosclerotic disease locally. In addition, the stent also included CD34-binding luminal antibodies functionalised to aid with re-endothelisation. Image drawn using the information provided in the study by Shah and Chandra [22], Wang et al. [25], Beshchasna et al. [26] and Hoare et al. [27].

out an *in vitro* investigation of the scaffold, culturing smooth muscle cells. An inner layer of poly (lactide-*co*-glycolide)/chitosan (PLGA/CS) aligned nanofibers were added to increase cell adhesion, induce optimal morphology and proliferation. This gave the scaffold an outside material with shape-memory ability and an inner layer to enable cell culture on the scaffold. As highlighted by the authors, this study is promising to produce scaffolds to be used in simulating small-diameter vessels. However, more work is needed before thicker vessels with scaffolds requiring more than two layers can be achieved. Initial *in vivo* study of the small-diameter vessels would be useful at this stage to ascertain compatibility of the construct within an animal model [31]. Fig. 3 shows how temperature can aid self-rolling of these artificial blood vessels.

Furthermore, a group working on poly (N-isopropylacrylamide) hydrogel-based tubes used alternative self-rolling triggers, UV light and magnetic fields [32]. By this method, magnetic nanorods were included in the hydrogel sheet, at varying concentrations across its geometry, so that when a magnetic field was applied, it could hold the tube in a flat orientation, and then when the magnetic field was removed, it spontaneously rolled into a tube [32]. An advantage of this technology over the other studies previously mentioned is perhaps that the deformation of the hydrogel — for example, its bending, single or double rolling, or helical twisting — can be tuned via the concentration of nanorods across the hydrogel sheet. The use of these nanorods allows application of this technique to other materials such as the hydrogel they used in this study do provide the potential to produce scaffolds with added features such as controlled drug release [32]. This study is certainly applicable in the context of different applications and materials.

An innovative solution to the problem of blood vessel tissue engineering is the development of electronic blood vessels. Cheng et al. incorporated a liquid metal conductive ink — composed of gallium-indium alloy and solvent, creating liquid metal particles of around 2 um diameter — into poly (L-lactide-*co*-ε-caprolactone) to create a biodegradable construct with encapsulated circuitry [33]. It was found that through electrical stimulation of the vessels, they could improve the process of endothelialisation, and for electroporation to allow gene delivery into certain parts of the blood vessel [33]. The construct had excellent biocompatibility and patency over a 3-month period post-implantation in an *in vivo* rabbit model [33]. This technology could lead to

Figure 3



a. The process of artificial blood vessels self-rolling under temperature-controlled conditions using poly (lactide-glycolide-trimethylene carbonate). Adapted from Chen et al. (2020) [31]. **b**. The process of artificial blood vessels self-rolling under UV light exposure and **c**. The artificial blood vessels before and after rolling. Adapted from Guo et al. (2020) [32]. UV, ultraviolet.

better personalised medicine, and, therefore, greatly improve diagnostics and treatments for cardiovascular health [33].

Heart failure

Heart failure can be caused by many conditions, but the most common cause is following a heart attack. This can arise when coronary artery disease is not treated in time, and a myocardial infarction occurs causing damage to the myocardium. The following section discusses how this damaged tissue can be treated.

Cardiac patches

The development of cardiac patches — a tissue engineered patch that is used to replace the area of myocardium that is damaged during a myocardial infarction — is a key research avenue for the treatment of myocardial infarction. A primary issue faced in the field of biomaterials and tissue engineering is the creation of vascularised tissue to deliver oxygen to all the cells in a construct. Moreover, where the damaged tissue is a result of hypoxia, for example with myocardial infarction, the tissue is oxygen deficient which causes oxidative stress and apoptosis of cardiomyocytes. Hence, the need to attenuate oxidative stress in this case is vital. Whilst the incorporation of endothelial cells into constructs with the aim of neovascularisation is a strategy used by many, this is not the only option for oxygen delivery [5]. In a study by Sheikh et al. (2022), the researchers developed an oxygen releasing antioxidant cardiac patch, made from antioxidant polyurethane with calcium peroxide incorporated as an oxygen generating material [5]. They found that this combination of materials provided a sustained antioxidant behaviour and release of oxygen, whilst inducing vascularisation, regeneration and decrease in oxidative stress [5]. Oxygen releasing calcium peroxide was incorporated within electrospun polyurethane fibres, enabling controlled oxygen release. Sustained release behaviour was demonstrated through the measurement of the kinetics of oxygen release over 10 days. The cardiac patch was also used for the delivery of exosomes

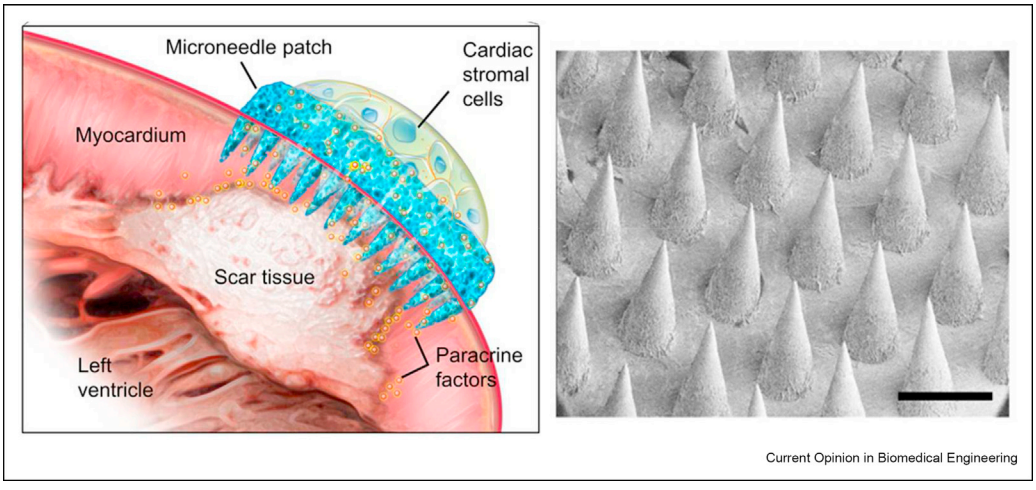
to treat MI, and when tested *in vivo* in a rat MI model. It was found to increase cardiac remodelling, angiogenesis and cardiac function. It also reduced oxidative stress and fibrosis found in the heart muscle, showing that, in addition to the benefit observed when other cardiac patches were trialled *in vivo*, the antioxidant nature of the patch further enhanced treatment of MI.

Bagdadi et al. produced a cardiac patch using neat poly (3-hydroxyoctanoate), P (3HO), with results showing that the material was as good as collagen in terms of cell viability, proliferation, and adhesion with no harmful effects on muscle contraction [34]. However, there are still issues that are faced before we can achieve an optimal patch design — primarily that patches either require surgical implantation and, therefore, a major surgery, or if they are injectable, they do not always maintain their function or shape. Researchers trying to tackle these problems have produced an injectable and conductive patch which exhibits shape-memory behaviour [35]. This patch was formed of methacrylated elastin and gelatin, with shape-memory behaviour exhibited through carbon nanotubules. They found that upon injection of the patch into a rat model of MI, there was some functional recovery, with the rat models having increased the ejection fraction and fractional shortening, as well as a decrease in infarct size [35]. This study also concluded with another *in vivo* study in a porcine model, and here they showed that the patch could be successfully delivered via a catheter under thoracoscopy, a minimally invasive technique. This shows great promise for the production of a MI regenerative treatment that does not require major surgery for implantation into patients.

In another interesting study by Tang et al. (2018), the researchers used a microneedle patch made of poly (vinyl alcohol) (PVA) to deliver secreted factors from cardiac stromal cells within the patch to the native tissue, with the aim of enhancing and promoting cardiac repair after MI [36]. The integration of cells delivered via transplanted epicardial patches is usually slow, and direct injection of cells into the myocardium often leads to poor cell retention; therefore, the microneedle technique is a potential solution to these problems [36]. The patch was made with 99% hydrolysed PVA with a micro-moulding approach, and the needles had a mechanical strength of approximately 2 N/m^2 which enabled them to penetrate through the tissue without breaking. This patch was tested on both rat and porcine MI models, with the rat model showing increased angiomyogenesis and cardiac functions, and the porcine model reveals no toxic results and furthermore the protection of cardiac function [36]. The microneedle patch design is shown in Fig. 4.

The first study reviewed in this work, looking at an oxygen-producing antioxidant patch, highlighted a valid limitation, in that this patch fails to deliver exosomes and oxygen beneath the outer layers of the heart muscle. It could be suggested that to progress this research, an approach such as the microneedle patch technique, designed to deliver factors for cardiac repair to within the heart tissue, could be a promising avenue. This microneedle technique then combined with the ability to inject a patch that has shape-memory, thereby mitigating the need for major surgery, could result in a much-improved overall design. With the current breadth of research into cardiac patches for the treatment of MI,

Figure 4



A Microneedle cardiac patch design for cell penetration into necrotic myocardial tissue. Scale bar 500 μm. Images taken from Tang et al. (2018) [36].

and many research groups exploring innovative and new patch designs, a combination of multiple designs might produce a patch that can provide all the benefits found in each of these studies.

Arrhythmias

There are many different types of arrhythmias, and for appropriate treatment to be provided, it is important to correctly identify the underlying cardiac rhythm disturbance that is causing the symptoms, to be able to target the therapy correctly. These types of arrhythmias can be life-threatening and this usually arises following a myocardial infarction. The current diagnosis is made using electrocardiograms, ambulatory monitoring in the form of Holter monitors or patches. These use surface electrodes stuck to the patient's skin that monitor depolarisation and repolarisation generated by the sinoatrial node and cardiac conduction system. However, they are prone to artefact through motion and electrode-skin interface impedance [37].

Arrhythmia detection

Recent advances have been made using stretchable conducting polymers as surface electrodes as they can conform to the skin without slipping, detaching or fracturing [37,38]. Initial versions of these electrodes were made into a mesh using gold as the conductive electrode which was a micrometre thick bilayer on layers of polyimide, Ecoflex substrate and water-soluble PVA substrate to make the sticker to which the electrode was attached [37,38]. This water-soluble PVA helped to reduce artefact from high signal to noise ratio as the PVA, once dissolved by water droplets on the skin surface, conformed to the skin, limiting slippage, detachment and fractures [37,38]. In addition to gold, silver has shown great promise as an electrically conducting nanomaterial when fabricated by electrohydrodynamic printing onto polyethylene terephthalate (PET) and polydimethyl-siloxane substrate [37,38]. Initially, the first-generation epidermal electronics were produced using photo-lithography on rigid wafers that could be easily handled. Subsequently, a rapid prototyping technique known as the dry and digital "cut-and-paste" method was introduced. This method involved the use of a paper/vinyl cutter plotter to subtractively pattern a bilayer of gold and PET on a temporary supporting substrate. The resulting fan-shaped mesh was then affixed to any desired target substrate, such as medical tape like Tegaderm [37,38]. These electrodes mentioned in the study were fabricated using this cutting and pasting technique and were therefore cheap to manufacture; however, one of the limitations of this cut and paste manufacturing is that the patterning resolution of the cutter plotter is limited to 200 μm. Recent studies have also used an atomically thin graphene as a conductive nano material layer as it has shown great promise due to its conductivity, biocompatibility, chemical inertness and mechanical robustness. However, current limitations with these graphene-based devices are poor skin adhesion [37,38].

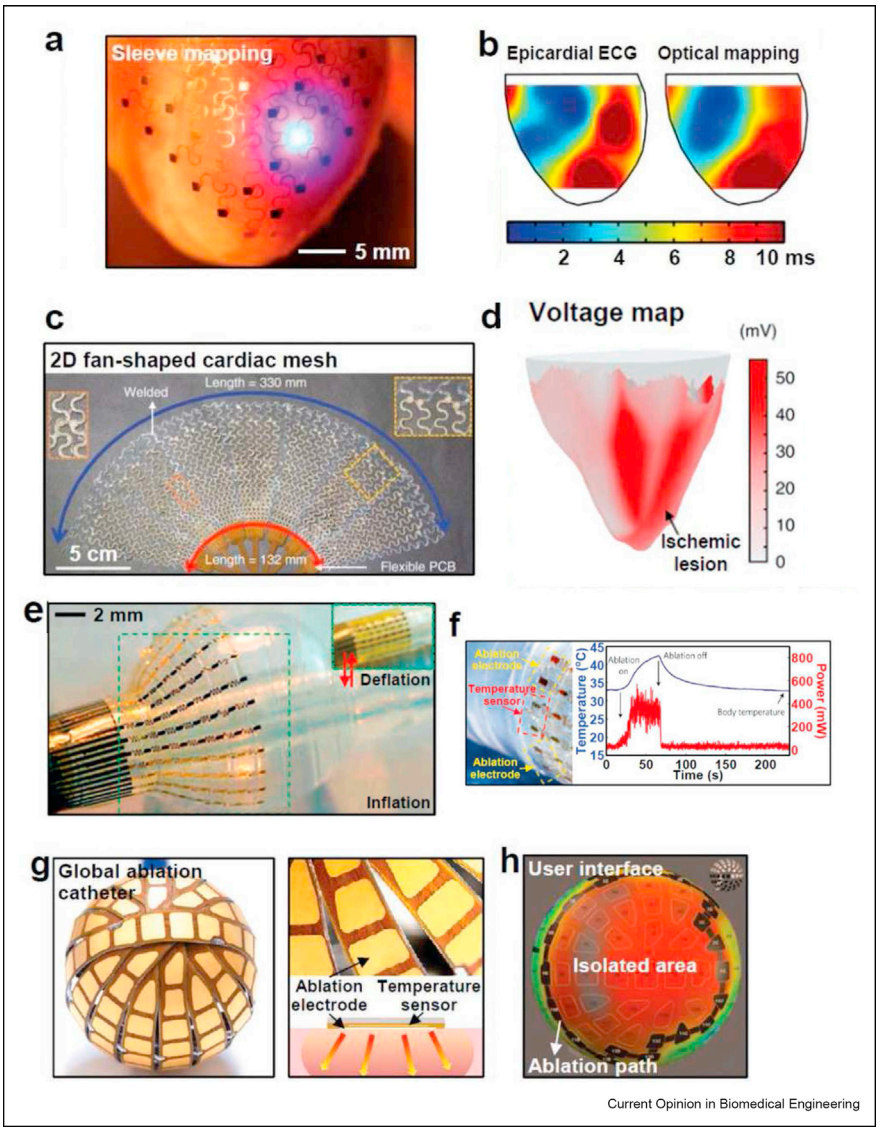
Despite these devices, some arrhythmias can still be difficult to capture, and electrophysiology studies may be conducted to identify exact origins of arrhythmias. Epicardial electrophysiological mapping can be extremely difficult to perform as most devices need total isolation from biological fluids. However, recently, there have been new developments using 288 multiplexed silicon nanomembrane channels which can be rolled up and delivered through a catheter [37,38]. These adhere to the epicardium using surface tension and can visualise cardiac depolarisation by the relative activation at each contact point; however, due to the reliance on surface tension, they can have poor contact with the epicardial surface and, therefore, exhibit poor reliability [37,38]. Therefore, 3D multifunctional integumentary membranes represent a breakthrough in soft epicardial electronics because they achieve spatiotemporal mapping across the entire epicardium, and they have been validated for their spatiotemporal mapping capabilities via *in vivo* experiments on rabbit hearts. A recent *in vivo* study in a pig's hearts has shown promising results using a cardiac fan-shaped mesh with 42 gold-coated silver nanowires in a styrene-butadiene-styrene elastomer [37,38]. The study showed that the mesh covered the entire ventricle with high conductivity and stretchability of up to 266%, and an *in vivo* voltage map was successfully conducted [37,38]. This shows great potential for future epicardial mapping.

Atrial fibrillation (a fast irregular heart rhythm) is another common arrhythmia which can be difficult to treat. Another study used a stretchable array of poly (3,4-ethylenedioxythiophene) polystyrene sulphonate for epicardial mapping of the atria in chronic atrial fibrillation [37,38]. The thin stretchable film helped mechanically coupled with the beating heart to give stable electrophysiological recordings with 2 times higher atrial-to-ventricular signal ratio and >100 times higher spatial resolution as seen in Fig. 5 [37,38]. though these *in vivo* studies have shown great promise, it is challenging to extend this to human cardiac models due to physiological differences, and therefore, further work needs to be carried out in this area by conducting more *in vivo* studies but in larger animals.

Arrhythmia management (ablation)

Once identified, the areas of abnormality that has led to atrial fibrillation can be ablated with current conventional therapy using a point-by-point ablation approach,

Figure 5



a) Cardiac sleeve mapping to detect sources of arrhythmias. (**b**) The map created from such a device when compared to conventional measurements shows high accuracy, (**c**) The fan shaped mesh with 42 gold coated silver nanowires in a styrene-butadiene-styrene elastomer. (**d**) A voltage map created using the fan shaped mesh, (**e**) An inflated and deflated image of a balloon ablation catheter with an array of sensors and actuators. (**f**) Temperature recorded by the ablation catheter from ablation (blue) and input power recording for radiofrequency ablation (red). (**g**) A clinically applicable global ablation catheter with in-built ablation and temperature sensors. (**h**) An image showing complete pulmonary vein isolation achieved using the global ablation catheter. These images are taken and adapted from Hong et al. (2019) [37].

whereby repeat procedures are usually required due to gaps in the ablation points. In recent studies, a new balloon radiofrequency ablation technique is able to isolate the circuit completely, leading to higher success rates and prevention of reoccurrence [37,38]. These soft bioelectronic integrated balloon catheters are flexible and stretchable with varying shapes and sizes of temperature sensors to monitor local temperatures during the ablation therapy. These new catheters have the ability to monitor local temperatures during ablation and could clinically improve efficacy and safety by controlling the time and size of the ablation [37,38]. These catheters are fabricated using a thin layer of titanium and platinum mounted on thin sheets of silk and can mitigate this need for repeat procedures as the temperature monitoring between two points of a radiofrequency catheter can be sensed to ensure full isolation of the circuit occurs between these points [37,38]. Alternatively, a very powerful clinically applicable global catheter consisting of 16 ribs, each of which contain 122 gold electrodes and flexible circuits for temperature sensing have been developed for pulmonary vein circumferential isolation [37,38]. This catheter has the capacity to monitor contact, temperature and

intracardiac electrogram sensing. This is achieved by monitoring the amount of contact (flow map), the electrogram amplitude (voltage map) and the propagation of the activation wave front (wave map) [37,38]. This aids with ensuring complete isolation of arrhythmias and is clinically translatable as the catheters have addressed a very common problem with current ablation techniques. However, one of the limitations that need addressing before clinical usage is their bulky size as seen in Fig. 5).

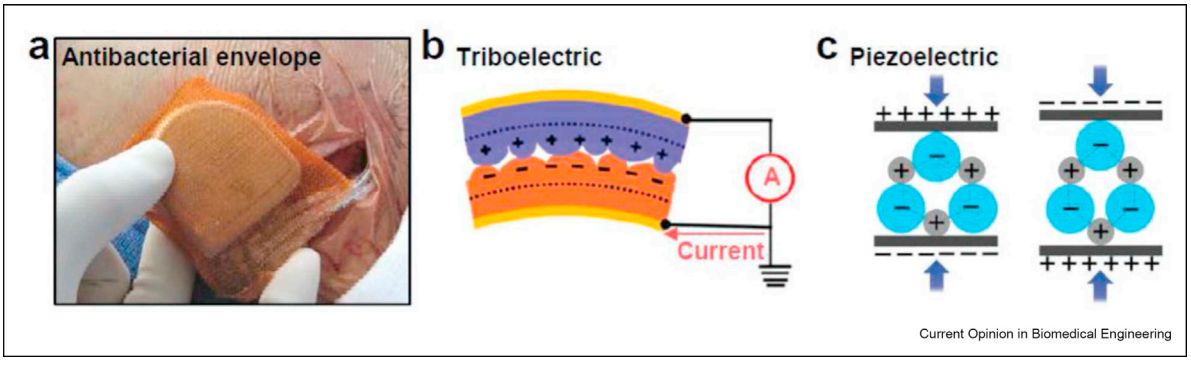
Cardiac devices — pacemakers and implantable cardiac defibrillators

One of the other methods used for treating arrhythmias apart from medication and ablation is the insertion of pacemakers. These devices consist of a generator and leads which are implanted underneath the patient's skin onto the patient's chest so that they can monitor the electrical activity of the heart and generate an electrical impulse when required. This treatment has been around for many years but is not a sustainable treatment option as the batteries of pacemakers require changing almost every 10 years dependent on patient usage. This battery change requires an invasive procedure and can increase the patient's risk of device-associated infections [39]. Cardiac implantable device-associated infections acquired during surgical procedures are major complications that are difficult to treat [39]. An antibiotic-eluting L-valine poly (ester urea) film has been developed to coat these devices for localised delivery of cefazolin and has shown promising *in vivo* results for the treatment of localised device pocket infections (infections occurring around the site of device insertion) [39]. Additionally, the Food and Drug Administration has approved a rifampicin and minocycline releasing poly (propylene)mesh to act as an envelope around devices for high-risk patients which aids with reducing device associated infections as shown in Fig. 6a [37,40]. However, this is still not a long-term viable treatment option as infections can still occur with device battery changes.

Studies have looked at two ways to reduce the need for battery changes for pacemakers and, therefore, reducing the risk of the above-mentioned infections. One technology is to use *in vivo* triboelectric nanogenerators using amine functionalised poly (vinyl alcohol) and perfluoroamine as triboelectric materials [6]. This technology uses body motion and gravity to recharge the pacemaker's battery, minimising the need for battery replacement surgery as shown in Fig. 6b [6]. Another study in rats used polydimethylsiloxane with a micropatterned pyramidal array of gold deposited within the polyimide substrate with aluminium foil and PET spacers as triboelectric nanogenerators [37]. The study showed that the movement generated from rats breathing was enough to produce enough electrical energy to pace the heart [37]. BC has been used in many studies with great success as the positive frictional layer of the triboelectric nanogenerator, as a way to increase the electrical output abilities of devices by producing a greater difference in potential across the generator [7].

Piezoelectric nanogenerators such as polyvinylidene fluoride-trifluoroethylene composites with zinc oxide and reduced graphene oxide alongside carbon nanotubes have also been used in studies [8]. Alternatively, molybdenum and poly (lactic acid) can be used for the piezoelectric nanogenerator [41]. This implantable polymer-based piezoelectric nanogenerator was able to use mechanical vibrations from the heart, lung and diaphragm to power the pacemaker, and as the pacemaker paced as shown in Fig. 6c, it used the heartbeat generated to harvest more electrical energy, making it self-powered and, therefore, reducing the need for battery replacement surgeries [8,41,42]. Although these studies have shown great promise for basic bradycardia pacing (slow heart rate), to apply this

Figure 6



a) Antibacterial envelop made of poly(propylene) mesh which releases rifampicin and minocycline to reduce device associated infections, (**b**) a schematic of energy harvesting mechanism of triboelectric nanogenerators using body motion and gravity, (**c**) A schematic of energy harvesting mechanism of piezoelectric nanogenerators using mechanical vibrations. Images taken from Hong et al. (2019) [37].

clinically to defibrillators, much more energy need to be generated and stored, making these devices bulkier.

Structural heart disease

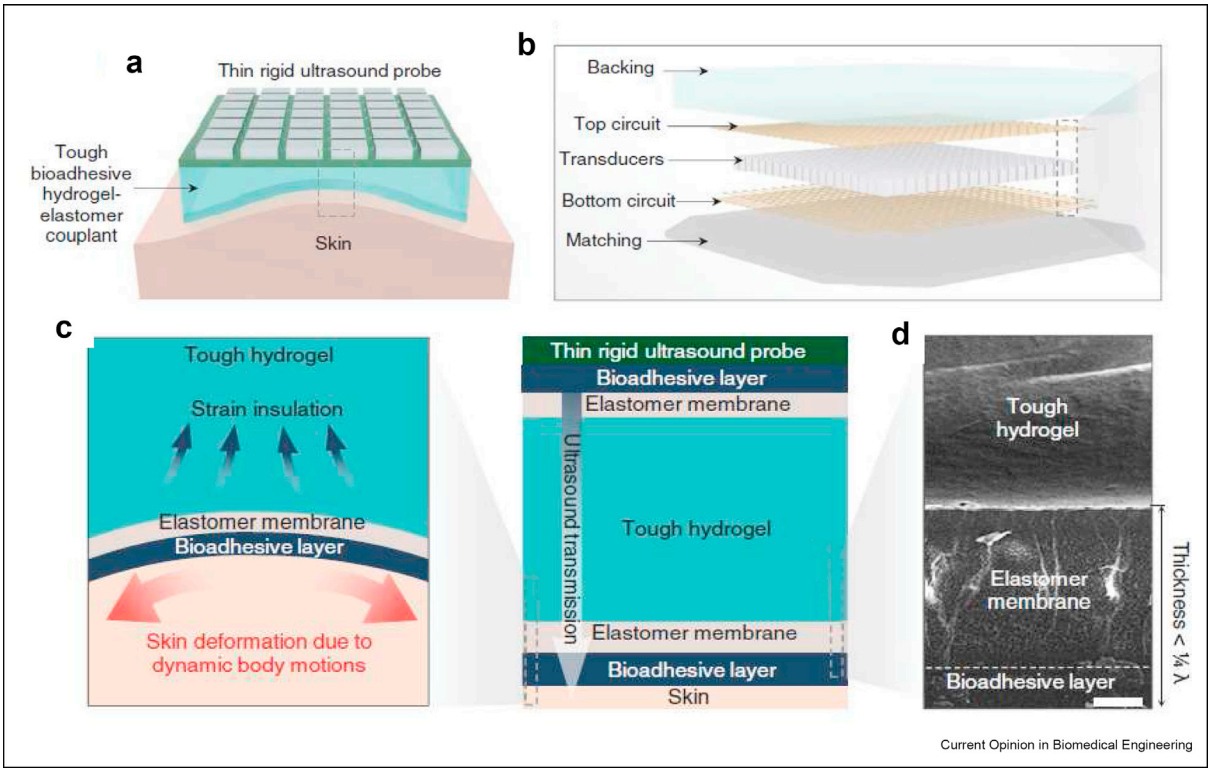
Structural heart disease represents a spectrum of conditions caused by a physical defect in the heart's structure and encompasses congenital heart defects which are present from birth through to degenerative changes that can occur with age [43]. At present, management for congenital heart disease is through various focused surgical or interventional procedures in early life to correct abnormalities [43] Whilst this approach is effective in addressing immediate haemodynamic and structural issues, long-term complications can develop either due to the underlying defect or as a consequence to the treatment offered [43].

Detection and management of congenital structural heart disease

The current diagnosis of congenital heart disease is mainly via transthoracic and transoesophageal echocardiography in combination with cardiac CT and cardiac magnetic resonance imaging [44–47]. Wang et al. recently developed a stamp-sized ultrasound scanner allowing continuous monitoring of organs such as the heart over a 48-h period [9]. This probe consists of a thin rigid piezoelectric transducer array which is coated in epoxy to prevent water damage and adheres to the skin using a multilayer hydrogel-elastomeric couplant [9]. The couplant consists of a tough hydrogel, containing 90 wt% water, which is further encapsulated by an elastomeric and bio-adhesive polyurethane [9]. This ultrasound scanner is made of a thin rigid piezoelectric ultrasound transducer array which can produce and detect ultrasound waves and is coated in epoxy to protect it from water damage. This stamp-sized ultrasound probe is then stuck to the skin via a soft bio-adhesive hydrogel–elastomer hybrid, made using layers of polyurethane and a hydrogel which is 90% water, enabling high-quality acoustic transmission to the skin, as seen in Fig. 7 [9]. Such devices can be extremely useful to monitor the exact physiology of congenital defects during day-to-day activities. Therefore, these ultrasound scanners could aid decisions for corrective surgery.

Going one step further in diagnostics, the addition of artificial intelligence and machine learning have shown great promise in foetal cardiology scans for the early

Figure 7



a) The stamp-sized ultrasound consists of a thin and rigid ultrasound probe adhered to the skin via a couplant and bioadhesive hydrogel-elastomer hybrid. (**b**) Schematics of the ultrasound probe structure which consists of an array of high-performance piezoelectric elements, which are controlled by the top and bottom circuits, which in turn are covered by acoustic backing layers. (**c**) The couplant is made using a hydrogel containing 90 wt % water encapsulated in an elastomeric membrane further coated by a thin bioadhesive layer (**d**) Scanning electron microscopy (SEM) image of the cross section of the hydrogel couplant. Scale bar is 10 μm. Images taken and adapted from Wang et al. (2022) [9].

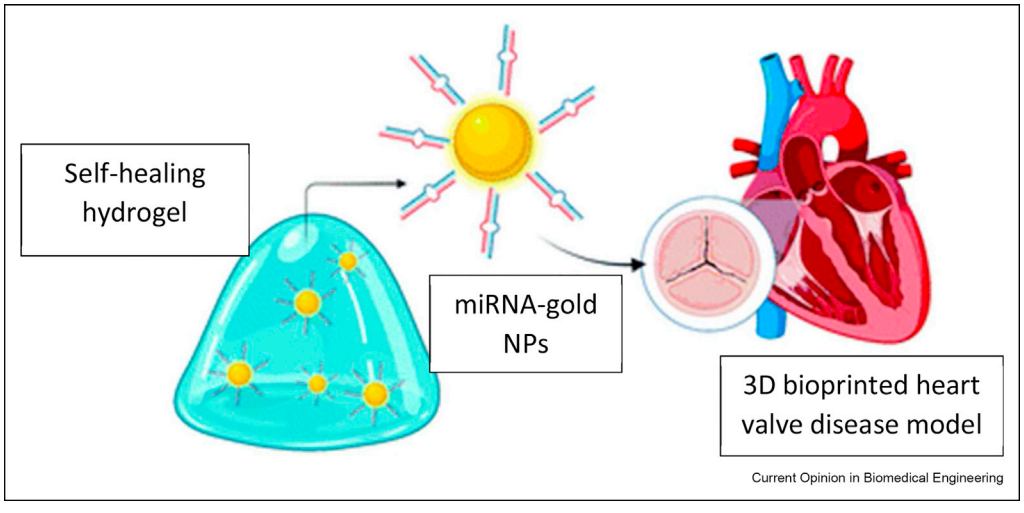
identification and diagnosis of congenital heart defects including *in utero* (in the womb) detection [45–48]. This is beneficial in order to plan management of such foetuses very early on in pregnancy. There have been several recent studies that have been able to use such diagnostic imaging to 3D-print the patient's exact anatomy using plastic (resin), silicone, nylon and polylactic acid, aiding clinicians to visualise the exact defects present and to plan and practice any surgical interventions required [46–48]. However, one of the limitations of this is that the materials used to print do not have mechanical properties matching that of human cardiac tissue, and therefore, suturing techniques can be difficult to practice on models as they can be too rigid or too easily tear with sutures. Nevertheless, this ability to visualise anatomy has also opened avenues for education and further treatment options including *in utero* surgery to increase chances of survival for complex congenital anatomical defects.

Treatment of degenerative structural heart disease — heart valves

Calcific aortic valve disease occurs in more than 25% of patients aged 65 or older, with valvular replacement representing a key treatment option for those with end-stage valvular disease [49,50]. The number of heart valve replacement surgeries is anticipated to increase from 200,000 to 850,000 annually by 2050, but this intervention is currently still associated with various adverse effects which impair the functional ability of the bioprosthetic implants used [49]. Various factors contribute to this, including implant calcification, immunogenicity, migration, and mechanical degradation; moreover, bioprosthetic implants lack regenerative abilities targeting local pathology. Tissue engineered heart valves (TEHVs) are a promising alternative which may address some of these issues. We present widely researched innovative solutions for mitigating these issues.

Many current TEHV constructs also suffer from calcification-driven leaflet maladaptation, occurring when resident valve interstitial cells (VICs) become osteogenic. Intelligent biomaterial–cell interfaces can affect cell-signalling via their chemical makeup or mechanical properties. Different approaches, therefore, exist to mitigate calcification of TEHVs. In order to produce a material with both nonlinear mechanical properties and resistance to calcification, Ma et al. developed a nanocrystalline cellulose hydrogel (mNG) through covalent conjugation of (2,2,6,6,-Tetramethylpiperidinyloxy)-modified nanocellulose (mNNC) onto the backbone of methacrylated gelatin (MeGel) [51]. Human adipose-derived mesenchymal stem cells encapsulated within mNG, down-regulated myofibroblast genes (SMA, MMP2) and osteogenic markers (Runx2, osteocalcin), both of which are associated with myocardial scarring and increased cardiomyocyte death. In addition, vimentin was upregulated, which indicated the presence of quiescent fibroblasts, a type of VIC present in the healthy cardiac cellular population. The presence of quiescent fibroblasts as opposed to myofibroblasts potentially indicates protection from calcification [51].This may stem from anti-inflammatory properties of nanocellulose [51]. The mechanical properties can be tuned depending on the amount of mNNC in the MeGel backbone, allowing further control of mechano-related signals by matching the stiffness of native valve tissue [51]. Although the study obtained excellent results, mNNC may demonstrate systemic toxicity *in vivo* and the degradation properties of mNG are unknown. Moreover, further studies in dynamic

Figure 8



The image shows how self-healing hydrogels with micro-RNA nanoparticles can be incorporated in 3D bioprinted heart valves to help treat diseased tissue and minimise calcification. Images taken from Van der Ven et al. (2021) [11].

Table 1

Summary of various cardiovascular applications, their associated problems and solutions that have been developed using intelligent biomaterials over the last 5 years. We also summarise possible areas for future work.

Problem	Solution	Future Work	References
Coronary artery disease treatment with coronary artery stents can lead to in stent restenosis over time	Coronary artery stents with CD34-binding luminal antibodies for promoting re-endothelisation; Poly (lactide-*co*-glycolide) nanoparticle drug delivery to treat atherosclerosis; Silicone and platinum biosensors to detect stent restenosis.	Coronary artery stent with CD 34 antibodies have been studied extensively but one of the current limitations is the control of proliferation of endothelial cells which needs to be studied further to prevent obstruction. The coronary artery stent biosensors have a lot of potential but to be able to detect in stent restenosis and clot formation, the sensor would need to be able to communicate outside of the vessel through multiple layers of tissue with varying permittivity and conductivity. Additionally, the biosensors would be near the hearts own conduction system and the episodic small voltages applied by the sensor to the vascular wall may have an effect on the hearts own intrinsic circuit. Additionally, preclinical validation using human vascular smooth muscle cells and endothelial cells *in vivo* prior to progressing the device to the next stage of development would aid translation into the clinic.	[22,25–27]
Artificial blood vessels/grafts for coronary artery bypass patients with unsuitable blood vessels for surgery	Shape memory scaffolds made of poly (lactide-glycolide-trimethylene carbonate, which can self-roll with temperature or hydrogel tubes which self-roll under UV light and magnetic fields and electronic blood vessels made using poly (L-lactide-*co*-ε-caprolactone) and liquid metal for endothelialisation.	The temperature-initiated self-rolling scaffolds need to be produced with a greater thickness in order to be used for more vessel applications. The UV/magnetic property-initiated self-rolling scaffolds have great potential for the incorporation of added features such as controlled drug release, which requires further research. Each of the studies in this section need to look further into *in vivo* assessment, with the self-rolling scaffolds initiating initial *in vivo* experiments, and the electronic blood vessels involving testing in a larger animal model.	[29,31–33]
Cardiac Patches for heart failure treatment	Injectable and conductive shape memory patches formed of methacrylated elastin and gelatin, with shape-memory behaviour, displaying carbon nanotubules or microneedle patch made of poly (vinyl alcohol) (PVA) for cell delivery or an oxygen releasing antioxidant cardiac patch, made from polyurethane with calcium peroxide.	A lot of research has gone into the development of cardiac patches, with lots of innovative solutions being tested. Of the recent studies reviewed in this article, a combinatorial approach to future research would be interesting. An oxygen-producing antioxidant patch that can benefit from microneedles to deliver oxygen plus other cardiac repair factors to deeper within the heart tissue would be an innovative patch for the future. In addition, the ability to be injected into the site of interest and then reattainment of its original shape, thereby mitigating the need for open heart surgery, would produce a patch with a whole host of benefits and improvements over previous designs.	[5,35,36]
Cardiac Arrhythmia Detection and Ablation Treatment	Stretchable conducting polymers such as polyvinyl alcohol with gold or silver as surface electrodes. Epicardial electrophysiological mapping using 42 gold coated silver nanowires in a styrene-butadiene-styrene elastomer or poly (3,4- ethylenedioxythiophene) polystyrene sulphonate and a global catheter consisting of 16 ribs containing 122 gold electrodes for temperature sensing during ablation to ensure full isolation occurs.	Many of the methods discussed for electrophysiological testing have shown great success within small animal *in vivo* models and more work needs to be carried out in larger studies for clinical translation	[37,38]

(*continued on next page*)

Table 1. (*continued*)

Problem	Solution	Future Work	References
Device associated infections due to pacemaker battery changes	Antibiotic-eluting L-valine poly (ester urea) (PEU) film to envelop pacemakers for localised antibiotic release for infection control; triboelectric nanogenerators using amine functionalised poly (vinyl alcohol) and perfluoroamine or polydimethylsiloxane with a micropatterned pyramidal array of gold deposited within a polyimide substrate with aluminium foil and polyethylene terephthalate spacers; piezoelectric nanogenerators such as Polyvinylidene fluoride-trifloroethylene composites with zinc oxide and reduced graphene oxide alongside carbon nanotubes or alternatively molydenum, Poly (lactic acid) and piezo poly-L-lactic acid can be used for the piezoelectric nanogenerator can make self-powered pacemakers.	Further work is required into triboelectric and piezoelectric nanogenerators to increase their generating and storage capacity as current work is focused mainly on small animal models. To be able to translate this clinically, larger animal studies with improvements in the amount of energy generated and stored by these nanogenerators, need to be conducted.	[6,8,39,41,42]
Congenital Heart Disease Diagnosis	Stamp sized ultrasound scanners using layers of polyurethane and a hydrogel which is 90% water, enabling high-quality acoustic transmission; artificial intelligence with machine learning for early diagnosis of congenital heart disease; 3D printing patient anatomy for surgical planning and practice.	Although the imaging resolutions of these bio-adhesive ultrasound scanners are superior to existing wearable ultrasound devices, the probe can be improved for better imaging quality in the future by reducing the pitches to eliminate artefacts and by introducing elevation focussing for deep organ imaging. Additionally, further work is required to reduce the size of the data acquisition system to enable the device to be clinically translatable.	[9,43–48]
Cardiac Valve replacements for degenerative disease	Anti-inflammatory properties of nanocrystalline cellulose hydrogel (mNG) through covalent conjugation of (2,2,6,6, -Tetramethylpiperidinyloxy)-modified nanocellulose (mNNC) onto the backbone of methacrylated gelatin (MeGel) can reduce valve calcification; micro-RNAs which have an anti-calcification effect; Self-healing shape-memory polymer via crosslinking of a carboxylate-dense PDMS polymer, with a Poly (ethylene-glycol) diglycidyl ether which can allow repair following damage caused by matrix remodelling or growth of TEHV.	mNNC may demonstrate systemic toxicity *in vivo* and the degradation properties of mNG are unknown, therefore further studies in dynamic environments as well as studies to verify the mechanisms of calcification protection are required. Additionally, more experimental work is required on the polymer, PDMS–COO–E. Although its mechanical properties show potential for cardiac applications, strain rate and direction experienced in physiological conditions is highly variable; and the potential effects of sheer stress have not been addressed. Furthermore, these properties may vary with geometry; the processability of the polymer has not been discussed, and the tested geometry did not mimic a TEHV-design, so further studies are required to address these areas.	[10,11,49–51,53–55]

environments as well as studies to verify the mechanisms of calcification protection are required.

Another difficulty faced by current valve replacement techniques is the ability to anchor the new valve in place, leading to implant migration. Self-adhesive biomaterials have been designed to address this issue [52]. PHAs, in particular medium-chain-length PHAs, have strong adhesive properties which can help anchor valves in place. These self−adhesive properties could be utilised to improve TEHV placement in the body, thereby decreasing implant migration. Furthermore, PHAs are bioresorbable and highly biocompatible; this encourages host tissue integration with the construct, which itself is resorbed by the body during planned degradation. This mitigates the requirement for permanent tethering and provides additional anchorage via additional cellular adhesion points compared to less biocompatible polymers.

Lai et al. produced a self-healing shape-memory polymer via crosslinking of a carboxylate-dense Polydimethylsiloxane (PDMS) polymer with a Poly (ethylene-glycol) diglycidyl ether [53]. This polymer, PDMS−COO−E, was highly elastomeric with an elongation at break of 290% at a strain rate of 100 mm min^{-1} or over 500% at 10 mm min^{-1} [53]. Although this does indicate potential for cardiac applications, strain rate and direction experienced in physiological conditions is highly variable; moreover, the study does not address potential effects of sheer stress. Furthermore, these properties may vary with geometry; the processability of the polymer was not discussed, and the tested geometry did not mimic a TEHV-design. PDMS−COO−E was able to autonomously self-heal repeatedly through abundant hydrogen bonding at 36% efficiency and demonstrated shape-memory effects between its T_g (0.5 °C) and 37 °C [53]. These properties may allow repair following damage caused by matrix remodelling or growth of TEHV, improvement of leaflet coherence and stent-less deployment via self-expansion, all of which are desirable qualities for TEHVs. Further testing is required before confirmation of these abilities; for example, via *in vitro* bioreactor studies. Moreover, although PDMS is widely used in biomedical devices due to its biocompatibility, no biocompatibility tests were conducted on this formulation, and biocompatibility tests of PDMS with cardiac cells are limited. Hofferberth et al. designed a geometrically adaptable pulmonary valve replacement inspired by venous valves using expanded polytetrafluoroethylene [54]. This valve accommodated the growth of juvenile sheep without trauma to surrounding tissue or loss of leaflet coaptation [54]. Although the ePTFE-valve required balloon expansion, similar geometry could be replicated using smart elastomeric biomaterials such as PDMS−COO−E or mNG, allowing autonomous *in-situ* expansion.

Micro-RNAs (miRNAs) are an attractive therapeutic target which can be incorporated into biomaterials to biochemically affect VICs. Cel-miR-67 is a non-biologically active miRNA sequence used as a control to determine whether a miRNA is able to be internalised from materials. Cel-miR-67 encapsulated in gold nanospheres within a biocompatible, shear-thinning and self-healing polymer-nanoparticle hydrogel (AuNP-miR-67-gel) was internalised by a 3D-bioprinted CAVD model as shown in Fig. 8 [12]. miRNAs implicated in anti-calcification effects include miR-141, miR-638 and miR-132 [10−12]. Such miRNA sequences could hence be incorporated into composite hydrogel TEHVs such as MeGel and consequently taken up locally by diseased tissue. Further studies are needed and overall, much work is needed prior to clinical translation or testing of smart TEHVs.

Conclusion

In this review article, we have discussed many cardiovascular diseases which have a high morbidity and mortality and we have described novel innovative polymeric biomaterials that have been designed recently with promising results that address the current treatment limitations. Cardiovascular diseases are very common and are the leading cause of death worldwide, with the main proportion of cardiovascular deaths due to myocardial infarctions and strokes. We have covered the development of better coronary artery stents that can limit thrombosis and in stent restenosis and thereby reduce myocardial infarction; the creation of artificial blood vessels which can act as coronary artery bypass grafts opening surgical options for complex patients and potentially increasing their chance of survival; cardiac patches that can treat heart failure which has unlocked more opportunities for better treatment and the potential to reduce morbidity.

We analysed many studies and summarised the significant progress that has been made with respect to complications associated with myocardial infarction, such as life-threatening arrhythmias, and how we can detect these successfully with pinpoint accuracy followed by targeted ablation or the implantation of cardiac devices for delivery of life saving treatment. Finally, we complete with structural heart disease diagnosis and potential treatment options ranging from congenital abnormalities diagnosed at a foetal stage through to degenerative changes with age. Throughout the article, we summarise and analyse novel biomaterials and highlight their clinical applications, limitations and what further work is required in the field. In conclusion, recent advances in engineering and materials have

helped us discover novel unique solutions for diagnosis and treatment of a variety of cardiovascular diseases and the combination of all these innovations shows great promise for the future of cardiovascular medicine. Table 1 summarises these various cardiovascular applications, their associated problems, current solutions available and where we see future research potential to allow these innovations to enter the clinic.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data was used for the research described in the article.

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In this study, the researchers developed an oxygen releasing antioxidant cardiac patch, made from antioxidant polyurethane with calcium peroxide incorporated as an oxygen generating material. They found that this combination of materials provided a sustained antioxidant behaviour and release of oxygen, whilst inducing vascularisation, regeneration, and decrease in oxidative stress

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