Nanotechnology in interventional cardiology: A state-of-the-art review

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ABSTRACT

Despite the contemporary techniques and devices available for invasive cardiology procedures, the current diagnostic, and interventional modalities have many shortcomings. As a contemporary cross-disciplinary technique, nanotechnology has demonstrated great potential in interventional cardiology practice. It has a pivotal role in detecting sensitive cardiac biomarkers, nanoparticle-enhanced gadolinium (Gd) contrast to enhance the detection of atherosclerotic cardiovascular disease (ASCVD), and multimodal imaging like including optical coherence tomography (OCT)/infrared luminescence (IR) for coronary plaque characterization. Furthermore, in invasive cardiology, the potential benefit is in miniaturized cardiac implantable electronic devices (CIEDs), including leadless pacemakers and piezoelectric nanogenerators to self-power symbiotic cardiac devices. Nanoparticles are ideal for therapeutic drug delivery systems for atherosclerotic plaque regression, regeneration of fibrotic cardiomyocytes, and disruption of bacterial biofilm to enhance and prolong the effects of antimicrobial agents in infective endocarditis (IE). In summary, nanotechnology-assisted therapies can overtake conventional invasive cardiology and expand the horizon of microtechnology in the diagnosis and treatment of CAD in the foreseeable future.

1. Introduction

Cardiovascular diseases (CVDs) are the primary cause of morbidity and mortality in the developed and the developing world. It is estimated to cause 18 million deaths this year and reach up to 23.5 million by 2030, contributing to approximately 32% of all global deaths, of which > 80% are due to acute myocardial infarction (AMI) [1,2]. The most common trigger for CVD is atherosclerosis, which is a cumulative disease process involving the harmful deposition of lipids and fibrous tissue within the arterial lumen. This causes a dysregulated immune response and altered cholesterol metabolism, leading to the formation of atherosclerotic plaques. These atherosclerotic plaques cause narrowing of the coronary arteries, resulting in oxygen demand and supply mismatch and myocardial ischemia, with subsequent disruption of the unstable lesions causing MI. This disease spectrum is called atherosclerotic cardiovascular disease (ASCVD) [3].

Apart from the secondary prevention of CVD, early diagnosis and primary prevention of CV risk factors are important for progressive coronary artery disease (CAD) [4]. With the advent of contemporary techniques in modern cardiology, diagnostic modalities and treatment practices have improved in the past two decades. Cardiac magnetic resonance imaging (MRI) and computed tomography angiography (CTA) have contributed largely to the noninvasive diagnosis of unclear cardiac pathologies and clinical treatment with pharmacotherapy has
improved the long-term prognosis and prevention of major adverse cardiovascular events [5,6]. Emergent percutaneous coronary intervention (PCI) can rescue cardiac ischemia caused by thrombotic occlusion in AMI by timely restoring patency of the coronaries. Moreover, cardiac implantable electronic devices (CIEDs) can prevent potentially fatal arrhythmias with permanent pacemakers (PPMs) and implantable cardioverter-defibrillators (ICDs), and help low functioning patients with heart failure achieve cardiac synchrony and alleviation of
symptoms with cardiac resynchronization therapy (CRT) [7]. Additionally, with advances in the understanding of the CV disease process, an increased number of studies are ongoing for unconventional techniques to diagnose, prevent, and manage myocardial dysfunction. This is because the mortality rate is still very high in cardiology practice, which indicates that the current clinical scenario can further be explored towards artificial intelligence (AI), micro, and nanotechnology [8,9].

Although devices and other stents are getting smaller exponentially as we progress in invasive cardiology, compared to these bulk materials, nanoparticles have a high surface-area-to-volume ratio. In addition, they can be altered in their biological properties, and have different shapes, sizes, and compositions [10]. These unique properties have granted the tools for scientists to devise novel therapeutic and diagnostic modalities that outperform traditional medicine. The main features, classification of nanoparticles, and their interaction with biological systems are shown in Fig. 1. In this review, we provide an in-depth overview of the available literature on the use of nanotechnology in interventional cardiology, summarizing the contemporary diagnostic and treatment methods. Furthermore, we discuss nanoparticle targeting strategies for specific identification of pathologic disease areas, followed by a state-of-the-art summary of nanomaterial-associated drug delivery systems and gene-targeting for the treatment of CVDs and cell regeneration. In the end, we describe the potential disadvantages and side-effects of nanotechnology.

2. Methods

The authors (T.A and R.H.) searched PubMed/MEDLINE, Scopus, CINAHL, Google Scholar, Web of Science, and independent websites for free-text words and Medical Subject Headings (MeSH) words as follows: “Nanotechnology” OR “Nanoparticles” OR “Nanotech” OR “Nanoscience” OR “Microengineering” OR “Nanomaterials” OR “Photonics” OR “Biotechnology” AND “Invasive cardiology” OR “Interventional cardiology” OR “Cardiovascular disease” OR “Atherosclerosis” OR “Atherosclerotic cardiovascular disease” OR “Coronary artery disease” OR “Valvular heart disease” OR “Endocarditis” OR “Cardiac implantable electronic device” OR “Cardiac pharmacotherapy” OR “Drug-eluting stents” OR “Drug-coated balloons” OR “TAVR” OR “MitraClip”. All article types were included with no language restrictions and selected, focusing on the following topics: pathophysiological mechanism behind ASCVD, endocarditis, and heart failure; use of nanotechnology in the diagnosis of major CVDs; nanoparticle-assisted cardiac biomarker detection and noninvasive molecular imaging; the role of nanoparticles in drug delivery to cardiac tissue, and the coronaries; nanoparticles targeting the inflammatory cells or pathological sites based on surface modifications; nanoparticle-assisted thrombolysis; nanoparticle-assisted biofilm intervention for endocarditis. All data was incorporated in a narrative fashion in the next sections.

3. Main text

3.1. Diagnostic potential of nanotechnology

3.1.1. Nanotechnology-assisted cardiac biomarker detection

The extent of success in treating CAD depends upon an early diagnosis, giving the patient a better prognosis, low morbidity, and mortality. When the myocardium is under stress or there is myocardial damage, the cardiac biomarkers, including cardiac troponins (cTns), myoglobin (Myo), and creatinine kinase MB (CK-MB), are released into the bloodstream [11]. To detect these biomarkers, a frequently used approach is mass spectrometry, however; it has certain limitations in sensitivity and specificity due to low plasma levels. Here, a combination of biosensors with nanotechnology can help detect CAD at an early stage. Fig. 2 shows biosensing methods by nanoparticles for prompt detection of cardiac biomarkers.

At first, protein polymers act as targets that are recognized by antibodies or aptamers, which are recognized quantitatively by various methods, including electrochemiluminescence (ECL), colorimetry, surface-enhanced Raman scattering (SERS), and electrochemistry (EC) [12]. The sensitivity of detecting biosensors can be greatly increased with the higher optoelectronic properties of nanoparticles. According to this principle, with the help of ZnSnO3, Singh, et al. designed an EC biosensor for the detection of TnT [13]. Similarly, the use of a gold triangular nanoprismon-based surface plasmon resonance (SPR) biosensor monitored TnT in the plasma, serum, and urine, making it 50-fold more sensitive than other techniques [14]. As nanoparticles have a high surface area to volume ratio, the porous structures can hold a large number of recognition elements and transducer proteins, resulting in

Fig. 2. Schemes of nanotechnology-assisted biosensors for detection of cardiac enzymes. (A) ZnSnO3 perovskite nanomaterial-decorated glassy carbon electrodes were designed as a label-free electrochemical biosensor to detect TnT. This method demonstrated a higher detection sensitivity owing to the ferroelectric property of ZnSnO3 [15]. (B) The gold triangular nanoprismon-based localized surface plasmon resonance biosensor monitors cTnT in plasma, serum, and urine. The cTnT assay becomes at least 50-fold more sensitive than other label-free techniques. (C) The nanodiamond hybrid hydrogen-substituted graphdiyne to construct electrochemical aptasensors for detecting Myo and cTnT. Created by J.M. with BioRender.com.
amplification of signal cascade. This theory was applied by Zhang, et al. into creating a nano-diamond hydrogen-substituted graphdiyne to amplify signals for detection of Myo and cTnI [15]. One other method of increasing detection sensitivity is through the modification of nano- materials to hold more signal transducer elements [16]. In addition, the shape of nanoparticles can optimize the detection sensitivity of cardiac biomarkers. El-Said, et al. designed a SERS sensor that consisted of a silver anisotropic nano-Pinetree array-modified indium tin oxide substrate for detection of Myo and CK-MB [17]. This substrate outperformed all other SERS sensors among nanostructure shapes. Early detection of raised cardiac biomarkers can help interventional cardiologists to screen high-risk versus low-risk acute coronary syndrome (ACS) patients and triage patients with increased cardiac biomarkers on priority catheterization schedules.

3.1.2. Nanotechnology-based imaging modalities

This section describes the important role nanotechnology can play in different imaging techniques for CVDs in cardiac catheterization laboratories and otherwise. Nanoparticle-based molecular imaging used in interventional cardiology is summarized in Table 1.

3.1.3. Cardiac magnetic resonance imaging

Magnetic resonance imaging (MRI) is a mainstream noninvasive imaging modality that has a wide array of functions in interventional cardiology, including abnormal blood vessels and atherosclerotic plaque quantification. When compared with nuclear imaging techniques like positron emission tomography (PET), MRI has a higher spatial resolution, and by employing three-dimensional time of flight (3D TOF) and spin-echo MR angiography, quantification of lipid core, fibrous cap thickness, and hemorrhage volume were determined in carotid atherosclerotic plaques efficiently [18–20]. However, the contrast agent detection of soft tissue is less sensitive compared with nuclear techniques. Therefore, nanoparticle-enhanced gadolinium (Gd) contrasts have been explored for molecular imaging in ASCVD and coronary thrombosis [21]. These nanoparticles on Gd produce a clear T1/T2-weighted image in cardiac MRI and small modifications on nano-level particles and biocompatible coatings increase MRI nanoprobes in ruptured or rupture-prone coronary disease for a longer circulation time [22,23]. These nanoparticles have paved a way forward for scientists to diagnose not only atherosclerotic plaque formation but related diseases such as inflammation and components of inflammation cascades.

An investigation was based on a design of highly sensitive magnetic iron oxide nanocubes (MIOns) for the identification of acute or chronic myocardial infarction (MI) [24]. Similarly, bioengineered hybrid metallic oxide-peptide amphiphile micelles (HMO-Ms) were investigated for atherosclerotic plaque and arterial thrombosis using MRI [25]. These HMOs were found to be compatible with aortic endothelial cells of mice and humans and their clot binding capability was 3x to 5x higher than their nontargeted counterparts, leading to early detection of hemorrhage in atherosclerosis. As platelets are inherently involved in different stages of atherosclerosis, their nano assembly with biomolecules can hypothetically localize atherosclerotic plaques [26]. These platelet membrane-coated nanoparticles showed affinity not only towards advanced plaques but also penetrated preatherosclerotic lesions.

3.1.4. Nuclear imaging techniques

Nuclear imaging is the most widely employed diagnostic modality before planning treatment by pharmacotherapy or revascularization. Hence, it is a widely ordered test among cardiac physicians, interventionalists, and surgeons alike. It has a high diagnostic yield, quantification capability, and functional detection [27,28]. F-fluorodeoxyglucose positron emission tomography (F-FDG PET) is the gold standard for diagnosing atherosclerosis, infective endocarditis (IE), vascular inflammation, and macrophage burden in the myocardium [29–32]. However, it is limited by its low spatial resolution of ≤2 mm with high metabolic myocardial uptake. This has restricted the use of F-FDG PET in cardiology practice. To overcome these limitations, nanoprobe-labeled with radiotracers and targeting elements have been investigated [33–35]. One such nanoparticle is the polymethyl methacrylate-core/polyethylene glycol-sulfonamide fractionated with viral macrophage inflammatory protein-II [36]. Another successful nanoparticle is the heavy-chain ferritin (HFn) radiolabeled with technetium 99 m used for unstable atherosclerotic plaques [37].

3.1.5. Multimodality imaging

In cardiology practice, each imaging modality has its unique advantages and intrinsic disadvantages. For a clinical diagnosis, MRI exhibits an excellent spatial resolution but has low sensitivity, while PET imaging demonstrates high sensitivity, but at the cost of ionizing radiation exposure and low spatial resolution. However, a fusion of both modalities yields better diagnostic information and is currently being employed in contemporary imaging technology [38–40].

The first diagnostic modality fusion was based on the nanoparticle-assisted PET/MRI dual-modal imaging method, which exhibited high spatial resolution of MRI and deep tissue penetration of PET [41]. In the near future, these multimodal imaging data can provide information on unconventional biomarkers implicated in a causal relationship with ASCVD and CAD. This was demonstrated by one group that reported an imaging technique based on myocardial cell-specific multimodal nano tracers [42]. These nano traces were derived from lipid-emulsion-based perfluoro-crown ether payload (19F-HDL) and named fluorophores. This multimodal imaging technique was a valuable addition to the cardiology toolbox in detecting atherosclerosis signals and the extent of coronary thrombosis. A contemporary biomedical imaging modality is photoacoustic (PA) imaging [43–45]. PA imaging uses a common signal detection marker with ultrasound imaging, therefore; it is a combination of high spatial resolution and conventional ultrasound penetration

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Table 1: Nanoparticle-based molecular imaging characteristics.

| Modality                        | Nanomaterials                      | Functions                              | Targets                      | Summary                                    |
|---------------------------------|------------------------------------|----------------------------------------|------------------------------|--------------------------------------------|
| MRI                             | Gd-TTP / LMWF-CNPs                 | Signaling P-selectin, cell penetration, Gd loading | Platelets and P-selectin ECs | Accumulation and visualization of atherosclerotic plaques and inflammatory endothelial cells |
| PAI                             | PBD-CD36                           | High targeting PA signals              | Inflamed cells               | Reflecting ultrasound waves on inflammatory areas in atherosclerotic plaques |
| Nuclear scintigraphy            | Ca-CANF-comb/Ag2S-Asgfl            | Cu for PET imaging, high targeting NPRC | NPRC                         | Assess the vulnerability of plaques and pathological functions of NPRC |
| Multimodal imaging              |                                     |                                        |                              |                                            |
| OCT/IR                          | IR-QD                              | OCT/PL signals                         |                              | Thrombin                                    |
| XEL/MRI                         | XEL-NCS                            | XEL/MI signals                         | Thrombus progression         |                                            |
| PAI/MRI/US                      | EHYW/DFe-Ink-PFHI                  | High targeting PAI/MRI/US              | Thrombus progression         |                                            |
| Ultrasound                      | NPs                                | signals                                | Activated macrophages and FRs | Vulnerable plaque visualization through activated macrophages |
| PAI/SPECT/CT                    | Au-PEG-FA                          | PAI/SPECT/CT signaling                 |                              |                                            |

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depth at a selective optical absorption [46]. Various nanoparticles have been used in PA imaging for the detection of CAD, including gold nanorods, gold nanocages, graphene oxide, and CuS nanoparticles [47]. Research has shown that iodine-doped gold nanoparticles can be used for myocardial stress imaging by PA imaging in mouse models (Fig. 3) [48].

Apart from these noninvasive imaging modalities, other nanotechnology-assisted combined schemes are being employed in experimental designs, including optical coherence tomography (OCT)/infrared luminescence (IR) and X-ray-excited luminescence (XEL)/MRI [49]. These modalities are used in the progression of thrombus and plaques in the coronary bed and can help interventional cardiologists to anticipate future events and the consequences of revascularization.

3.2. Nanotechnology-based therapy

This section will be dedicated to the nanotechnology approaches applied in the treatment available of core interventional cardiology as well as the broad discipline of general cardiology-related therapies based on nanomaterials’ physicochemical properties and surface modification.

3.2.1. Nanotechnology-assisted therapy for valvular heart disease

Heart valves are made up of different structures and each one has its histological profile. Although the pulmonary and aortic valves as well as the mitral and tricuspid valves reflect similarity in their structure, they are individually designed to ensure optimal function concerning their role in the cardiovascular cycle [50]. Mature heart valves are composed of an extracellular matrix that is aligned with interstitial valve cells surrounded by an endothelial cell layer. The valves are divided into layers of elastin, proteoglycan, and collagen that provide distinct biomechanical properties to leaflets and their supporting structures [51]. Vascular heart disease (VHD) is prevalent in many parts of the world, and the leading problem is either senile degeneration or rheumatic fever-related valve damage [52]. Currently, prosthetic valves (mechanical and bioprosthetic) are the mainstay of treatment for VHD, but they have several complications, including increased risk of endocarditis, higher bleeding risk, and valve thrombosis. Valve replacement using a bioprosthetic valve usually results in a rapid ectopic calcification and its durability is shortened due to its tendency to mechanical failure. On the other hand, the replacement of mechanical valves requires long-term anticoagulant treatment and may be subject to life-threatening hemodynamic failure [53]. Therefore, there is an urgent need to develop new therapies that can help reduce or overcome current problems. The nano-technological techniques for treating heart valve diseases involve the use of tissue engineering, to produce a fully functional heart valve and the use of Nanoparticles to alter the structure and behavior of damaged valves [54]. For this, the Silsesquioxane nanocomposite polymer’s anti-calcification effects were investigated which demonstrated that nanocomposite had a lower calcification rate when compared with glutaraldehyde-fixed bovine pericardium and polyurethane valves. Therefore, Nanocomposite can be considered a viable candidate for contemporary valve replacement surgeries. Nanotechnology carries great potential in valve design, particularly for smaller individuals with small dimensions because it allows the formation of unlimited sizes and individualized unique properties and structures. Therefore, this nanocomposite with structures that mimic cardiovascular tissue can be considered as an alternative for cardiovascular tissue and heart valves [55]. The University of Texas Health Sciences (San Antonio, TX) produced a nanosynthetic valve (Perc Valve), made of eNitinol. The developed prosthesis had a monolithic design that emulated the physiological function of the native valve. The leaflets

![Fig. 3. Measurement of myocardial stress using iodine-doped gold nanoparticles and photoacoustic imaging. Gold nanorods are commonly used as photoacoustic (PA) contrast agents. Previously Au/Ag activatable nanoparticle has been reported to respond to reactive oxygen and nitrogen species (RONS) using PA. RONS can selectively etch off the shell while leaving the gold core intact. The etching results in the reactivation of the PA signal. Iodide-doping of silver increases sensitivity to RONS, thus physiologically relevant levels can be detected in a mouse model. Adapted from “Iodide-Doped Gold Nanoparticles to Measure Oxidative Stress Using Photo-Acoustic Imaging (PA)”, by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.](https://app.biorender.com/biorender-templates)
Consisted of microporous membranes with an ultrathin diameter of < 10 µm that allowed fast endothelialization. Similarly, Sutherland, et al. developed the first autologous tissue-engineered valve prosthesis composed of bone marrow-derived stem cells [56]. This can be a pioneer for the development of tissue-engineered aortic and mitral valve prostheses and needs structural and particulate development for optimal results. In the era of percutaneous CV interventions, nanoparticles might be of particular importance in catheterization laboratories. Tissue-engineered transcatheter aortic valve replacement (TAVR) devices could be a breakthrough approach for treating aortic valve stenosis. Recent advances in polymeric valve technology facilitate designing more durable designs with minimal in vivo adverse reactions. A paper published on 23rd March 2022 has demonstrated 900 million cycles of accelerated durability testing (equivalent to 20 patient-years) for a polymeric TAVR device [57]. The first-generation device has optimized performance, including a reduction in polymer material volume for a lower crumpled delivery profile and a stent frame that gives an optimized radial force with lower material volume, securing robust deployment and anchoring. As indications for TAVR are expanding rapidly, this bioengineered optimization method employed in polymer

Fig. 4. Biofilm formation cycle and therapeutic target sites for biofilm disruption by nanoparticles in endocarditis. Adapted from “Biofilm Formation Cycle”, “anti-Biofilm Therapeutic Target Sites”, by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.
technology serves to establish polymeric TAV devices as an alternative to the current TAVR devices.

3.2.2. Nanoparticles for biofilm disruption in infective endocarditis

The healthy cardiac endothelium is protected by antibacterial films to resist the entry of pathogens. However, after the endothelium is damaged by inflammation, sclerosis, and direct bacterial activity; infective endocarditis (IE) occurs with a change in the endocardium, including the platelet and microorganism-rich vegetation [58–60]. With the accumulation of microorganisms to thrombus, the vegetation biofilm becomes mature and causes embolism, demonstrating the stigmata of IE [61]. A biofilm is considered a cooperative microbial community that is surrounded by a self-produced extracellular matrix [62]. They can also affect the opening and closing of the valve, leading to valve regurgitation or stenosis. General antibiotics do not affect all microorganisms in the biofilm, as a result; more complications, such as heart failure, abscess formation can occur. Moreover, the detached biofilm can embolize the peripheral circulation [63].

Studies have shown that diverse transport proteins recognize and transport substances through the bacteria and cause antibiotic resistance [64]. Therefore, effective pharmacotherapy requires the selection of the most appropriate antibiotics and drug delivery for a prolonged period. This increases the risk of toxicity to the patients. For this reason, several nanomaterials have been used for drug delivery to the infected sites while others alter the bacterial cell wall and disrupt the normal functions of the microorganism. Several metallic nanoparticles, including silver (AgNPs), gold, copper, and zinc (ZnO), inhibit biofilm formation [65–68]. AgNP can eradicate biofilms of Escherichia coli by damaging the membrane, therefore increasing the membrane permeability [69]. ZnO forms reactive oxygen species and causes membrane disorganization, inhibits protein expressions and affects cellular functions [70]. Fig. 4 shows biofilm formation and therapeutic target sites for nanoparticles.

To perform as a novel drug-delivery system, several nanocarriers have been used for different types of pathogens (Table 2). These carriers are hollow or porous in characteristics, making a high surface area to volume ratio. Therefore, these nanocarriers improve the stability of drugs and prolong drug circulation by acting on the particles in different environments and providing a sustained drug release. This decreases the administration frequency and in turn, the drug’s side effects [71]. Arul Selvaraj, et al. showed that copper oxide nanoparticles, in combination with amoxiclav deliver a significantly improved minimum inhibitory concentration against Proteus mirabilis [72]. Similarly, the effectiveness of polymyxin B delivered through AgNP is improved several times against P. aeruginosa [73].

At present, several nanoparticles are developed against Staphylococcus aureus (S. aureus) biofilm showing enhanced antimicrobial activity. Mihu, et al. developed nitric oxide (NO)-releasing nanoparticles against S. aureus for rat central venous catheter infection [74]. NO can kill bacteria by inactivating enzymes responsible for biofilm formation, showing that these nanoparticles can have an implication in the treatment of IE. Similarly, mupirocin nanoparticles have shown a higher survival rate compared with free mupirocin against S.aureus infections. Additionally, the combination of nano-mupirocin with nano-liposome increased and prolonged mupirocin drug levels in the plasma [75].

Nanoparticles can also be used for prosthetic valve endocarditis. Studies report the application of antimicrobial nanoparticles on prosthetic valves to prevent infection after valve replacement surgery. Angelina, et al. covered the prosthetic valve with pyrolytic carbon and AgNPs to prevent bacterial colonization [76]. AgNPs act as synthetic endothelium by affecting bacterial viability to the prosthetic valve material and pyrolytic carbon prevents adherence of the bacteria to the surface. Therefore, nanoparticles with antimicrobial properties show promise for the contemporary treatment of IE and other chronic infectious diseases.

3.2.3. Nanotechnology and cardiac implantable electronic devices

Since the first pacemaker insertion in 1958 by Dr. Senning, there have been major developments in CIED technology, including a reduction in size, battery extension, remote monitoring capacity, as well as MRI-compatibility [77]. Despite advancements, conventional CIEDs have inherent limitations and a potential for complications due to the creation of surgical pockets and placement of epicardial or transvenous leads [78]. These complications often lead to a considerable increase in morbidity, mortality, and healthcare expenditure [79]. The leadless pacemaker is emerging microtechnology that has the potential for reducing right ventricular lead-associated complications [80]. At present, two leadless systems have been approved for implantation in humans: the Nanostim leadless cardiac pacemaker and the Micra transcatheter pacing system [81]. The Nanostim implantation started in early 2013 but it was recalled due to premature battery failure and issues with some docking button separation from the device [82]. However, the Micra AV, a single chamber device with the advantage of achieving atrioventricular synchrony, was approved by Food and Drug Administration in 2020 [83]. While these devices decrease the risks of conventional pacemakers, they also have their own set of complications and long-term implications [84]. However, small non-randomized trials have established their safety and efficacy in worldwide registries [85–90].

Other examples include the experimental symbiotic pacemakers and piezoelectric nanogenerators which are self-powered using the biomechanical energy from the cardiac and respiratory movements [91]. Implantable nanogenerators are designed for long-term in vivo cardiac implantation providing the muscle to CIEDs by gathering biomechanical energy and eliminating the need for batteries. The best performing piezoelectric materials are lead-based ceramics. At present, their use is limited in humans because of the toxicity and requirement for flexibility in CIEDs [92].

3.3. Coronary artery disease and nanotechnology

3.3.1. Nanoparticles in the treatment of atherosclerosis

By activation of endothelial cells in arterial walls, the initial stage for plaque formation is set by the attraction of monocytes and their migration to the intima. These monocytes mature and form foam cells by uptake of cholesterol deposits. Further progression occurs with the migration of smooth muscles fibers and assembly of extracellular matrix, leading to a central region of necrosis and a fibrous cap on the plaque. Over time, the plaque becomes unstable with thinning of the fibrous cap and progressively increasing size of the necrotic core, leading to plaque rupture and AMI [93].

Nanoparticles are potential candidates for the treatment of atherosclerotic plaques by increasing the fibrous cap thickness and plaque regression by decreasing the central necrotic area [94,95]. Fig. 5 shows the use of nanodisc carriers to enhance cholesterol transport and reduction of coronary plaques, gene modulation for decreased plaque accumulation, and apoptosis of damaged cardiomycocytes for regeneration of new cells. These nanodiscs deliver therapeutic biomolecules to
the site of coronary atherosclerosis and shrink plaques by reducing inflammation, and bringing about the removal of cholesterol crystals and lipids [96]. sHDL, polyethylene glycol, and poly lactic-co-glycolic acid have emerged as biodegradable delivery systems for a controlled drug-release of anti-inflammatory materials (Ac2-26 peptide and interleukin-10 cytokine) and drugs (statins) [97,98]. In vivo delivery of interleukin-10 can increase the fibrous cap thickness and decrease the necrotic core in a mouse model of atherosclerosis [99]. The major limitation to the implementation of nanoparticles in the treatment of coronary atherosclerosis is a lack of understanding of the long-term biological effects of these materials on the human body. More specifically, nanoparticles form a protein corona when in contact with biological fluids, which has not yet been adequately investigated in cardiac nanotechnology.

3.3.2. Role of cardiovascular regenerative medicine with nanoparticles

Several studies have shown that novel nanotechnologies stimulate angiogenesis from vascular or pluripotent stem cells [100]. This can have various implications like wound healing, recellularization of whole organs, and regeneration of cardiomyocytes. Fig. 6 shows a simple process of decellularization of damaged organs followed by recellularization.

An undifferentiated population of cells derived from subcutaneous fat (stromal vascular fraction) is reported to promote cellular detachment from the extracellular matrix which in turn enhances the secretion of vascular endothelial growth factors (Fig. 6). Seeding of stromal vascular fraction nanomaterials enhances blood perfusion recovery in a mouse model of peripheral arterial disease [101]. Similarly, engineered vessel grafts show a promising alternative to autografts in coronary artery bypass surgery. Tan, et al reported that bioengineered anthracene-grafted styrene-block-butadiene-block-styrene enhances the proliferation of human umbilical vein endothelial cells [102]. This approach can have larger ramifications in CV engineering.

Over the past decade, cardiomyocyte regeneration had been focused on cell-based repair [103,104]. These techniques are limited by poor grafting of the therapeutic cells in heart tissue, lack of accurate in vivo monitoring, and potential for arrhythmic complications. Nanoparticles are significantly useful to overcome these limitations of patient-specific therapeutic cells by targeting the part where cell damage has occurred [105]. This can enhance the therapeutic efficacy of pluripotent stem cells. Fig. 7 gives an overview of the cardiomyocyte regeneration process with induced pluripotent stem cells through forming nanoplatforms to create cells with improved therapeutic potential. However, the only drawback of this technique is that a substantially low percentage (<1%) of the administered cells reach their therapeutic peak (see Fig. 8).

The current literature on nanotechnologies in CVDs is focused on paramagnetic iron oxide nanoparticles [106]. This is because of their
biocompatibility and diagnostic as well as therapeutic implications in regenerative CV medicine. There are reports, however; that these nanoparticles activate tumor-associated macrophages [107]. Therefore, further investigations are needed to investigate their hypothetical role in worsening CV inflammation, which can lead to an increased cell rejection by the hyperactive immune system. Further work needs to be considered before the implementation of CV regenerative medicine as a potential specialty in the future.

3.3.3. Nanotechnology-assisted percutaneous coronary intervention

The advent of drug-eluting stents (DES) solved the problem of instantaneous restenosis, however; there remains a potential complication of
Fig. 7. Showcase of the effect of nanomaterial in cell regeneration with Wnt signaling to enhance the therapeutic efficacy of cardiomyocytes with iPSCs. Nanomaterial scaffolds can be used to culture the desired tissues needed for repair in an organ and promote angiogenesis. Adapted from “Nanoparticle Signaling During Cardiomyocyte Differentiation”, by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates.
stent thrombosis after PCI. Stent thrombosis has been described to occur in 0.5 % – 2 % of patients undergoing PCI [108,109]. It is divided into early, late, and very late stent thrombosis and is usually multifactorial, including (but not limited to) drug compliance, strut apposition, P2y12 inhibitor resistance, multiple stents, low ejection fraction, etc. [110,111]. To prevent stent thrombosis, systemic drug delivery had exhibited success in thrombosis and restenosis rates following PCI. However, systemic drug delivery is mostly inadequate and requires higher doses which can produce side effects in humans. This provides a rationale for the development of materials that can be delivered precisely to the desired area.

The most recent DES technology constitutes dual-therapy stents that incorporate two therapeutic agents like aspirin and adenosine diphosphate-receptor blockade for antiplatelet activity [112]. Furthermore, the new bioresorbable vascular scaffolds mitigate the risk of thrombosis, since their implants degrade over time and leave an intact vessel [113]. Meanwhile, bio-engineered stents include a nanoparticle, cell capture technology, or autologous venous tissue for better therapeutic effects [114]. In addition to stent design and material innovation, the newer stents also use different coatings to enhance the surface properties and clinical behaviors. This allows a higher concentration of the drug localized at the specific site [115]. Although these molecules exhibit good therapeutic effects, they still have some limitations due to high costs and safety issues.

Other novel techniques include the use of porous or microporous balloons evaluated for local drug delivery. With these devices, nanoparticles, adenoviral vectors, and oligodeoxynucleotides have been successfully delivered in animal models [116]. The efficacy and safety of porous balloons vary greatly among different devices, drugs delivered, and the size of the nanoparticles. A major disadvantage of these balloons is an increased intimal thickening due to high delivery pressures and large volumes of perfused nanoparticles in the coronary arteries. However, the delivery of antisense phosphorodiamidate morpholino oligomer demonstrates decreased restenosis in human coronary arteries but due to technical difficulty in crossing the lesion and lesser drug delivery to the media and intima, this device has not gained popularity.

Compared to porous balloons, drug-coated balloons are less traumatic and offer a homogenous drug delivery into the vessel wall with low-pressure inflation [108]. There is a myriad of literature available on drug-coated balloons in acute and chronic coronary syndromes. In the PEPCAD-2 ISR trial, a drug-eluting balloon was non-inferior in terms of the primary outcome when compared with paclitaxel-eluting stents [117]. However, in the PEPCAD- trial, when compared with sirolimus-eluting Cypher stents, drug-eluting balloons did not achieve non-inferiority and target vessel revascularization rates were doubled [NCT00473499]. Similarly, delivery of paclitaxel using a double-balloon perfusion catheter failed to show any advantage over bare meral stents in porcine coronary arteries [118]. Table 3 shows targets for nanoparticle-facilitated drug delivery in coronary CAD.

### 3.4. Toxicity of nanoparticles

When compared with other types of CV biomaterials, the toxicity of nanoparticles is more important because of their mobility in the body. It is well known that safe biocompatible nanomaterials are used for their synthesis, but toxicity is mostly attributed to the nature of their components. Many studies have reported cytotoxic activities of nanoparticles, despite their clinical ramifications in CVDs [119]. It was demonstrated that paramagnetic iron oxide can cause in vivo thrombosis, platelet aggregations, reactive oxygen species formation, and cell death [120]. Pulmonary inflammation and cardiomyocyte toxicity have been observed with zero-valent iron nanoparticles [121]. It causes an increment in oxidative hazard when it is exposed to human A549 and EA.hy926. Despite the immense potential of iron nanoparticles in the human body, their safety should be tested before commercial use. This concern is also applicable to carbon nanoparticles, about a decreased viability in aortic endothelial cells and inhibition of platelet aggregation [122]. Furthermore, increased atherosclerosis is observed with direct
monocyte adhesion to endothelial cells. Moving forward, atherosclerosis can itself cause various CVDs. Acute phase reactants have been enhanced after carbon nanotubes treatment, which itself is a risk marker for CVDs [123]. Even bio-inert nanomaterials like gold nanorods have been shown to cause cellular toxicity, including DNA damage, and nanomaterials used in regenerative treatment for cardiac fibrosis have potentially toxic effects on intra- and extracellular levels resulting in dysfunction of signaling cascades [124]. Future research is needed to fully investigate the potentially harmful effects of nanoparticles on hemotoxicity and inflammatory responses. Also, further investigations should focus on techniques and methodology to make nanotechnology safe for human beings.

4. Conclusion and future perspectives

Nanotechnology as the technological driver of advancement has paved a promising avenue in the treatment of CVDs because it can increase the efficacy of conventional cardiology material. There is a gradual implementation of CV biomedical implantation techniques in recent years. The most promising breakthrough is the nanosized drug-delivery systems on implantable stents and drug-coated balloons to tackle CAD. The use of nanotechnology on a metallic stent enhances cell response in the vessels and through increased proliferation and adhesion of endothelial cells, the process of re-endothelialization can take place. This mitigates the potential risk of stent thrombosis and in-stent restenosis, enhancing the activity of the treated vessels. Beyond coronary arteries, nanotechnology has also taken part in regenerative medicine through stem cells, contributing to early wound healing, recellularization of whole organs, and regeneration of cardiomyocytes. Targeted drug delivery has been a noteworthy potential of nanotechnology, because of its outstanding multi-functionality. This technique has contributed to the disruption of bacterial biofilms in the treatment of drug resistance in IE and preventing IE in prosthetic valves by their resemblance to CV tissue, inhibiting bacterial invasion on the prosthetic valves. Nanomaterials are involved in the evolution of precise biosensors for the detection of CAD biomarkers, leading to enhanced diagnostic sensitivity, and shortened diagnostic time. In the future, these nanomaterials can be used in hospitals, ambulances, and other medical clinics. In comparison to conventional imaging techniques in cardiology, nanoparticle-based molecular imaging probes can specifically load themselves at the site of atherosclerosis or cardiomyocyte injury through modification on the surface of nanoparticles. Despite all the potential benefits, future investigations should consider several implications of nanotechnology-assisted CVD treatment. First, there should be controlled use of nanoparticles, especially those with potential toxic effects on myocardial cells. Secondly, the introduction of contemporary delivery approaches to CV target sites, and utilization of stent-coating technologies should be upscaled to an industrial level. Moreover, the interaction of nanoparticles with cells and cellular uptake should be studied for nanoparticle-associated complications and long-term effects.

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 paper.

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