International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 4, 2023

Review Article

NANOTHERANOSTICS IN CARDIOVASCULAR DISEASES: A NOVEL TOOL

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Received: 08 Feb 2023, Revised and Accepted: 12 Apr 2023

ABSTRACT

The leading cause of mortality worldwide is cardiovascular disease (CVD). Myocardial infarction, ischemic heart disease, ischemic injury, damaged arteries, thrombosis, and atherosclerosis are among the heart and blood vessel issues referred to as CVD. The most prevalent cause of CVD is atherosclerosis, an inflammatory disease of the arterial blood wall. Because of the complexity of CVD, pathophysiology, diagnosis, and therapy remain vital issues. The inadequacies of current treatment and diagnostic methods have given rise to theranostic nanomaterials. "Theranostic nanomaterials" describes a chemical with dual uses, including therapeutic and diagnostic applications. Theranostic nanoparticle imaging contrast can be advantageous for computed tomography (C. T.), positron emission tomography (P. E. T.), and magnetic resonance imaging (M. R. I.).

Additionally, they can cure CVD by employing medication delivery by nanoparticles or photothermal ablation. This study reviews the prevalence of the most recent developments in theranostic nanomaterials for identifying and treating CVD following the order in which diseases advance. Theranostics techniques for CVD detection include M. R. I., CT, near-infrared spectroscopy (NIR), and fluorescence. There have also been discussions of other theranostic nanoparticle-based CVD therapeutic methods.

Keywords: Nanotheranostics, Cardiovascular diseases, Nanocarriers, Imaging

DOI: https://dx.doi.org/10.22159/ijap.2023v15i4.47521. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Keywords such as cardiovascular diseases, theranostics, and atherosclerosis were used in popular web libraries such as Scopus, Pubmed, and Google scholar for procuring the articles from various periods, and the most relevant ones were used in developing this manuscript.

The phrase "cardiovascular disease" refers to various conditions that affect the heart and blood arteries [1]. It need not just cause harm to the heart; it may also affect other organs [2]. It entails irregular heartbeats, plaque buildup in blood vessels of the heart or any other organ, issues with the heart's ability to contract and relax, tightening of valves or leakage through valves, irregularities with the heart's lining muscles, as well as other congenital issues [3]. The four main categories of cardiovascular diseases are as follows: a) Coronary heart diseases, which result from an imbalance between the oxygen supply and demand to the cardiac muscle; b) strokes and transient ischemic attacks, which happen when the blood supply to the brain is temporarily reduced (in the case of a stroke) or completely cut off (transient ischemic attacks) c) Peripheral arterial disease brought on by the accumulation of plaque or a reduction in blood flow in the peripheral arteries (limbs) d) Aortic disease develops when the blood flow to the aorta is interrupted or considerably diminished [2]. The most prevalent cardiovascular disease is atherosclerosis. It starts slowly with the aggregation of lipoproteins in the blood arteries, forming clusters and oxidizing them into oxidized lipoproteins. The endothelial cells emit signaling chemicals as a result. These signaling chemicals attract monocytes and help macrophages develop. Macrophages can ingest only a specific quantity of oxidized lipoproteins before they reach their capacity and die. These dead macrophages are referred to as foam cells. The development of a necrotic lipid core is caused by these foam cells. Platelets are drawn to this necrotic lipid core and release growth factors produced from platelets. This growth factor encourages the development of smooth muscles, which release collagen, proteoglycans, and elastin, forming the fibrous cap and the first plaque. The calcium released by the oxidized lipoproteins during this period causes the plaque to calcify.

Additionally, the presence of macrophages causes inflammation, which in turn causes a stable plaque to develop. When the fibrous cap randomly splits, exposing the foam cells, a blood clot forms, increasing blood vessel blockage. The different stages of atherosclerosis progression are depicted in fig. 1. Cardiovascular diseases refer to a wide range of illnesses caused by atherosclerotic plaque that cause cellular damage and tissue death in the heart or other organs [4-6].

Ethnographic prevalence of cardiovascular diseases globally

According to the World Health Organization, cardiovascular illnesses claimed the lives of 17.9 million people worldwide in 2019, accounting for almost 16% of all fatalities, approximately one-third of those under 70. According to gender statistics, men comprise 52.2% of the population, while women comprise 42.2% [7, 8]. Table 1 summarizes the number of fatalities throughout the various WHO regions.

Table 1: Estimated deaths due to cardiovascular diseases in different WHO regions

Region	Total	Male	Female	References
Global	1,78,63,827	93,23,254	85,40,573	[8]
Africa	10,93,577	5,35,505	5,58,073	[8]
America	20,23,079	10,41,640	9,81,439	[8]
South East Asia	39,39,886	21,54,102	17,85,784	[8]
Europe	38,74,816	17,86,750	20,88,065	[8]
East Mediterranean Region	14,64,671	78,74,88	67,71,83	[8]
West Pacific Region	54,67,799	30,17,770	24,50,029	[8]

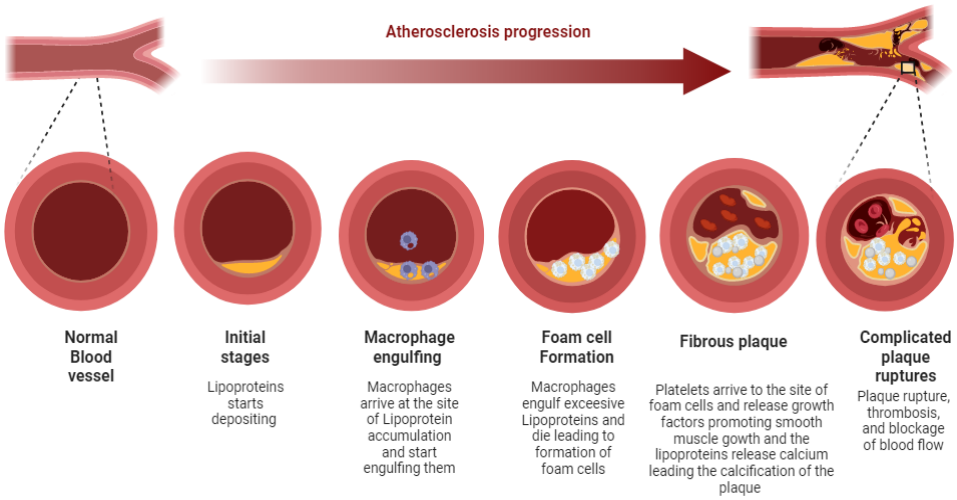

Fig. 1: Different stages of atherosclerosis progression [4-6]

The West Pacific region has the highest share of all the regions, accounting for 30.6%, followed by the South East Asian region (22%), Europe (21.6%), the Americas (11.3%), the East Mediterranean region (8.19%), and Africa (6.12). The East Mediterranean region has the second-lowest share of all the regions, and Africa has the lowest percentage, 6.12%. Males comprise around 52.2% of the world, while females comprise about 47.8%. Table 2 summarises the estimated global fatalities by gender and age for men and women [8].

Table 2: Age/Sex-wise estimated deaths globally

Age group	Male	Female	References
0-28 d	473	384	[8]
1-59 mo	13,717	12,363	[8]
5-14 y	11,867	11,270	[8]
15-29 y	81,558	47,981	[8]
30-49 y	7,05,599	3,39,840	[8]
50-59 y	11,91,369	6,31,284	[8]
60-69 y	20,58,547	12,97,136	[8]
70+years	52,59,823	62,00,315	[8]

Ischemic heart disease and stroke account for around 49.7% and 34.6% of fatalities overall from cardiovascular illnesses, respectively. Table 3 summarises the estimated global mortality from various cardiovascular diseases [8].

Table 3: Estimated deaths based on different cardiovascular diseases globally

Disease	Total	Male	Female	Reference
Rheumatic heart disease (1.6%)	2,88,348	1,25,943	1,62,404	[8]
Hypertensive heart disease (6.4%)	11,48,939	5,07,943	6,40,996	[8]
Ischemic heart disease (49.7%)	88,84,887	48,47,657	40,37,229	[8]
Stroke *(Ischemic stroke/Hemorrhagic stroke)* (34.6%)	61,93,978 *(30,72,131/31,21,847)*	31,60,831 *(14,77,581/16,83,250)*	30,33,147 *(15,94,551/14,38,596)*	[8]
Cardiomyopathy, Endocarditis, Myocarditis (1.9%)	3,49,908	2,07,698	1,42,210	[8]
Other vascular diseases (5.5%)	9,97,768	4,73,181	5,24,587	[8]

Tables 4 and 5 summarize the anticipated mortality rates for various age groups owing to various cardiovascular illnesses in both the male and female populations [8].

Table 4: Estimated deaths of different age groups of males due to various cardiovascular diseases globally

Disease/Age group	0-28 d	1-59 mo	5-14 y	15-29 y	30-49 y	50-59 y	60-69 y	70+years	Reference
Rheumatic Heart Disease	0	913	2,419	9,802	20,729	18,795	25,391	49,165	[8]
hypertensive Heart Disease	0	0	13	2,173	27,361	52,735	99,910	3,25,751	[8]
Ischemic Heart Disease	0	0	61	33,693	3,94,226	6,74,589	10,89,524	26,55,565	[8]
Stroke*(Ischemic Stroke/Hemorrhagic Stroke)*	76 (26/50)	4,949 (657/4,292)	4,914 (405/4,509)	22,888 (2,723/20,165)	1,92,540(27,767/1,64,773)	3,67,152 (83,107/2,84,044)	7,22,232 (2,78,293/4,43,940)	18,45,980 (10,84,601/7,61,378)	[8]
Cardiomyopathy, Endocarditis, Myocarditis	153	4,605	1,987	7,463	40,084	35,152	40,660	77,594	[8]
Other Vascular Diseases	144	3,251	2,743	6,539	30,659	42,947	81,130	3,05,768	[8]

Table 5: Estimated deaths of different age groups of females due to various cardiovascular diseases globally

Disease/Age group	0-28 d	1-59 mo	5-14 y	15-29 y	30-49 y	50-59 y	60-69 y	70+years	Reference
Rheumatic Heart Disease	0	1,031	2,507	7,598	25,074	25,066	30,129	70,199	[8]
Hypertensive heart disease	0	0	14	1,850	20,300	43,278	89,821	4,85,732	[8]
Ischemic Heart Disease	0	0	51	16,578	1,46,524	2,86,880	6,03,806	29,83,990	[8]
Stroke *(Ischemic Stroke/Hemorrhagic Stroke)*	129 (97/92)	3,694(639/305)	3,931 (350/3,581)	12,908 (2,025/10,082)	1,13,299 (16,882/96,417)	2,36,262(44,517/1,91,746)	4,99,766 (1,69,185/3,30,581)	21,63,157 (13,60,915/8,02,242)	[8]
Cardiomyopathy, Endocarditis, Myocarditis	117	3,924	1,828	3,629	14,697	13,052	18,609	86,353	[8]
Other vascular diseases	137	3,715	2,938	5,418	19,945	26,744	55,005	4,10,684	[8]

Risk factors

Genetics

Since cardiovascular disorders are characterized by nucleotide polymorphism, genetics may have a role in a person's potential development of these conditions. Cardiovascular illnesses can be monogenic (caused by a single gene), oligogenic (caused by several nucleotides), or polygenic (caused by several nucleotides). Examples of this criterion include the presence of xanthomas and variant APOB, LDLR, and PCSK9 genes inherited by people with familial hypercholesterolemia, which causes substantial elevations in low-density lipoprotein cholesterol levels (patches of cholesterol buildup). People with primary hypertriglyceridemia may have genetic polymorphisms in L. P. L., APOC2, LHF1, and APOE, as well as severe APOE mutations. Familial HDL is a rare genetic disorder that results in deficient levels of HDL in the blood and is thought to be caused by variations in the ABCA1 and APOA genes [9]. Patients with obstructive coronary artery disease were shown to have higher single nucleotide polymorphisms of ADAMTS7. Additionally, individuals with peripheral artery disease had it overexpressed [10].

Gender and age

Compared to women of the same age, younger males are more likely to have cardiovascular illnesses. However, the situation has changed because cardiovascular problems affect women more frequently than males their age after menopause [6, 11]. However, compared to women, males have an earlier decline in subclinical testosterone levels, which results in an earlier start of cardiovascular illnesses. According to Stanchewciz *et al.* and Vitale *et al.*, the years immediately after menopause often manifest cardiovascular problems in women [11, 12].

Obesity

Because obesity triggers a similar cascade of atherosclerosis development, where free fatty acids and oxidized lipoproteins start to deposit, leading to plaque formation, obesity is a significant risk factor for cardiovascular illnesses [13, 14]. According to Csige *et al.* (2018), obesity can also result in diastolic dysfunction, myocardial fibrosis, atrial fibrillation, and heart failure.

Smoking

Smoking significantly impacts the development of cardiovascular disorders and their commencement. It results in higher oxidation of atherogenic lipids, lower levels of high-density lipids, and a procoagulant character, all contributing to atherogenesis [15, 16].

C-reactive protein and low-density lipids

Blood levels of low-density lipids significantly contribute to the development of cardiovascular illnesses. They often have a linear relationship with heart disease. Another biomarker for cardiovascular disorders is the C-reactive protein. It was formerly believed that the relationship between LDL and C-reactive protein was linear; however, several investigations have shown that C-reactive protein is an independent biomarker. Patients who have excessive blood levels of LDL may not always have elevated levels of C-reactive protein and thus are at intermediate risk. Patients with increased blood levels of C-reactive proteins and LDL are at the most significant risk [17-19].

Current treatment for atherosclerosis

Various medications can be administered to treat the illness depending on the underlying cause and the conditions that make the plaque more likely to develop. In high-risk and urgent situations, surgical techniques are used.

Medications

The primary factor causing atherosclerosis and its progression is lipid deposition. Drugs that assist lower blood levels of low-density lipids may be able to ease artery inflammation or dissolve fatty deposits. Blood clots are the main problem that results from atherosclerotic plaque. Low-dose aspirin treatment can aid in preventing these problems. Although they might not be able to stop plaque or clot development, medications that lower high blood pressure may assist in avoiding subsequent issues [20-22].

Surgical procedures

A thin, flexible tube is inserted through a major blood artery during the angioplasty and stent replacement process and then guided to the target location. A wired mesh (stent) is then inserted to ensure that the artery stays open after the obstructed artery has been opened using a balloon. During coronary bypass surgery, blood arteries from the leg, arm, or chest are removed and replaced with healthy blood vessels that are then sutured together to reroute the blood flow. With the use of a blade or laser at the end of a catheter, the plaque is reduced in size or vaporized into tiny fragments during an atherectomy, a minimally invasive operation. But in contrast to the other two operations, it is ineffective [21].

Drug-eluting stents

Sustained-release medicine is placed on bare metal stents to stop blood clotting within the stent. To avoid restenosis, the drug-eluting stents are retained in place. However, because blood thinners are frequently chosen as the medication of choice for coating stents, usage is restricted, especially for those with bleeding issues [22].

Theranostics

The name "theranostics" is created by fusing the words "treatment" and "diagnostics." It is a method that tries to administer the diagnostic and therapeutic agents in a single dosage, as the name indicates. Theranostics aims to combine imaging, a therapeutic agent, and a biomarker and deliver them together to gain knowledge about the detection of diseases, the progression of conditions, the efficacy of the medication given, and planning for improved or similar therapies in the future [24-27].

To do this, the necessary compounds are conjugated using nanoplatforms, increasing the delivery's accuracy. Fluorescence-based imaging agents, magnetic resonance imaging (M. R. I.), near-infrared imaging (NIR), computed tomography (C. T.), and other imaging agents based on imaging systems can all be utilized [28]. Similarly, nanoplatforms can occasionally be employed directly in treatment or imaging when metal structure gold nanoparticles are used with C. T. or Photothermal (PTI) agents [29-31]. Fig. 2 is a general representation of the Nanotheransotic particle.

Role of nano theranostics

Routinely administering cardioprotective medicines has certain drawbacks, including limited solubility, poor bioavailability, non-specific action, less precise targeting, and a shorter half-life [30]. We can achieve selective targeting, tracking, or monitoring the drug delivery, a higher drug load, increased penetration, controlled release, enhanced biocompatibility, tuneability, and surface

functionalization by designing a nanocarrier to carry both the diagnostic and the therapeutic molecule. As a result, Nanotheranostic allows us to provide the therapeutic molecule for a specific condition while also diagnosing it [32-34].

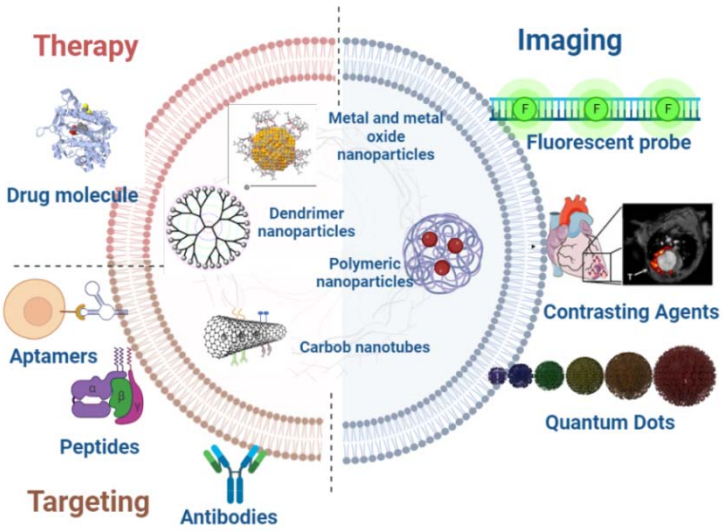

Fig. 2: Theranostic nanoparticle [24-31]

Different types of theranostic nanoparticles

MRI-based nanotheranostic particles

A high-density lipoprotein-like magnetic nanostructure (HDL-MNS) was created by Nandwana *et al.* Its iron oxide magnetic nanostructure core was coated with phospholipids and ApoA1 to resemble HDL. These HDL-MNS had an effective M. R. I. contrast and a cholesterol efflux rate comparable to native HDL at 4.8% [35]. Ouzmil *et al.* created solid lipid nanoparticles loaded with ultrasmall superparamagnetic iron oxide and the medication prostacyclin. These particles displayed 2.6-fold stronger contrast than clinically utilized superparamagnetic agents and had an inhibitory impact on platelet aggregation [36]. Wu. Y. *et al.* created nano cocktails with cerium oxide and iron oxide; cerium oxide was used because it can self-regenerate anti-ROS while transitioning from its trivalence and tetravalence states. Cerium oxide and iron oxide were used in cell M. R. I. experiments as effective contrast agents. *In vitro* tests also showed a considerable decrease in the R. O. S. levels in activated macrophages [37]. Another study by Wu Y *et al.* created nanocomposites employing layered double hydroxide as carriers containing CeO2 and Fe3O4 and found that they effectively quenched R. O. S. while producing a strong M. R. I. signal. Additionally, fumagillin was created and linked to paramagnetic perfluorocarbon nanoparticles for targeted drug administration and improved M. R. I. signals. Following these findings, the authors noted that the iron oxide nanoparticles were more sensitive than the paramagnetic perfluorocarbon nanoparticles [38].

Fluorescence-based nanotheranostic particles

Lu *et al.* produced selenium-based photodynamic multi-layered nanoparticles with chitosan, Royal Bengal, and glutathione as the first coating. This primary layer was then recoated with carbonyl groups from hyaluronic acid and folic acid covalently coupled with amine groups of ethylenediamine (SENPs). Hyaluronic acid and folic acid were ligands to bind to the surface-located CD44 and folate receptor beta (F. R.). By converting H2O2 to O2, SENPs reduced inflammation by lowering the amounts of both H2O2 and activated macrophages. According to Lu *et al.* (2017), LDL-stimulated macrophages showed a more significant fluorescence rise than unstimulated macrophages [39]. Dextran sulfate-deoxycholic acid (DS-DOCA) nanomaterials with chlorin e6 as the photosensitizer was created by Yi *et al.* ater 2 min of laser irradiation, it was discovered that 80% of the macrophages underwent cell death [40]. Hou *et al.* created a nano gel using curcumin as the photosensitizer and oligomeric hyaluronic acid-2-[propane-2-acid-2-diyllbls (thio)] diacetic acl-hydroxymethyl ferrocene (HASF@Cur). When HASF@Cur was delivered to atherosclerotic rat models, it resulted in fewer lesions and more fluorescence in macrophages [41]. Kosuge *et al.* reported on preparing single-walled carbon nanotubes with Cy 5.5 dye for photothermal ablation and NIR imaging. According to ex vivo research [42], carbon nanotubes exhibited significant fluorescence and apoptotic properties. Marrache *et al.* and Sun *et al.* reported on two quantum dot models. Sun *et al.* created a nanoparticle-based on the simian virus 40 packed with quantum dots and labeled with cyclic peptides. By concentrating on the p32 protein, it was planned to deliver the Hirulog peptide to macrophages. Stronger fluorescence in plaque and targeted delivery of Hirulog protein were both seen in studies using ApoE (-/-) mice [43]. With triphenyl phosphonium, apolipoproteins, and Qdot® 705 ITKTM amino P. E. G. quantum dot core, Marrache *et al.* created a synthetic HDL nanoparticle with improved lipid targeting and degradation that had HDL-like characteristics [44].

Computed tomography (C. T.) based nanotheranostic particles

Qin *et al.* reported the fabrication of gold nanorods for theranostics of inflammatory macrophages; micro-CT findings demonstrated that a rise in signal was dependent upon concentration and that macrophage damage was shown by histological results [45, 46].

Photoacoustic-based nanotheranostic particles

Gao *et al.* targeted the transient receptor potential cation channel by conjugating a monoclonal antibody with copper sulphide and a photoacoustic agent (TRPV1). In imaging, NIR showed a robust photoacoustic signal. For 12 w, the atherosclerotic buildup was reduced in Apo E knockouts [47].

CONCLUSION

These pre-clinical investigations suggest that Nanotheranostic particles can effectively cure cardiovascular disorders, particularly atherosclerosis, which appears to be the leading cause of their problems. The therapeutic medication and imaging component seem to be successfully encapsulated or adsorbed by nanocarriers, which then convey them to the target with the aid of a signaling molecule. Imaging techniques include M. R. I., photoacoustics, fluorescence, near-infrared radiation, computed tomography, and fluorescence. Iron oxide has a higher sensitivity than paramagnetic perfluorocarbon nanoparticles, making it the preferred material for M. R. I. Metallic nanoparticles, such as gold nanoparticles, are helpful for imaging and thinning plaque. Copper sulfide was an efficient photoacoustic agent that provided signals for plaque imaging.

Although every result was successful, the methods the cells use to take them in are unclear. The main difficulty in theranostics is creating a product that can be mass-produced, has high dependability, and is economical. Theranostic in the field of CVD is still in its infancy compared to what is known about it in the field of cancer. More research is required to create models that closely resemble atherosclerosis in humans.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

FUNDING

Our study was supported by grants from the JSS-AHER DBT BUILDER: Sanction order No: BT/INF/22/SP43045/2021.

ACKNOWLEDGMENT

The authors would like to thank the Department of Science and Technology–Fund for Improvement of Science and Technology Infrastructure in Universities and Higher Educational Institutions (DST-FIST), New Delhi, for their infrastructure support to our department.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest.

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