INTRODUCTION

Worldwide, cardiovascular disease (CVDs) is the leading cause of death for both females and males. CVDs were responsible for 32 percent of all global fatalities in 2019, according to estimates. Inflammation of the artery wall leading to atheromatous plaque development produces atherosclerosis, one of the most important causes of CVDs. Atherosclerosis is a chronic disease of the arterial wall that results in arterial wall thickening. First, atheromatous plaques ultimately break, leading to blood clots in the artery lumen above the ruptures, even though atherosclerosis is generally asymptomatic for years or even decades. Stenosis (narrowing of the artery) or worse, total closure of the artery results in inadequate blood flow to tissues and organs after blood clots have healed and shrunk. Another risk factor for an aneurysm is excessive compensatory arterial expansion. Stroke, coronary artery disease, and peripheral vascular disease are clinical manifestations of this. All CVD deaths are caused by heart attacks and strokes, which account for 85 percent of all deaths.

Emerging Nanoparticles in the Diagnosis of Atherosclerosis

Tanushka Kataria, MD Sadique Hussain*, Gurleen Kaur, Anuska Deb
School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India.
*Corresponding author’s E-mail: sadiquehussain007@gmail.com

Received: 11-07-2021; Revised: 25-09-2021; Accepted: 30-09-2021; Published on: 15-10-2021.

ABSTRACT

Throughout the last few decades, cardiovascular research has substantially advanced our awareness of the atherosclerotic process, the molecular processes underlying the disease remain essentially unexplained. Atherosclerosis results from the unbalanced lipid metabolism and lipoproteins accumulation that results in the thickening of the artery walls, linked to most cardiovascular events, and also one of the foremost common causes of morbidity and mortality around the world. Despite the extensive investigation into the process of development and advancement of atherosclerotic lesions over the years, there is little information is available. The use and handling of nanotechnology on a molecular scale is a new approach to quantify the functional organization in nanometers. In medicine, it is capable to improve diagnostics, delivery of pharmaceuticals, treatment, and many areas of research, development, and clinical application. Medical nanotechnology or nanomedicine has demonstrated a growing trend in the reduction of costs and improve the efficiency of current medicines, diagnostic reagents, implants, etc. Nanomedicine overcomes certain problems of conventional drugs like drug toxicity and the required dose of the drug. Promising research has resulted in pre-clinical validation of nanoscale devices targeting cell and molecular components of atherosclerotic plaque in the past decade. This review paper will cover basic insights into the use of nanomedicine in atherosclerosis

Keywords: Nanomedicine, Targeting, Diagnostic, nanoscale.

QUICK RESPONSE CODE →
DOI: 10.47583/ijpsrr.2021.v70i02.008
DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v70i02.008

It is not until the arteries are substantially constricted or obstructed that the initial symptoms of atherosclerosis become apparent. Atherosclerosis causes different signs and symptoms in different arteries. Some common symptoms are angina, numbness, dizziness, arrhythmias, shortness of breath, weakness.

It is now possible to employ atherosclerosis-related information for diagnostic and therapeutic purposes because of advancements in cellular and molecular understanding and nanotechnological developments. Clinical methods to atherosclerosis can be improved by using nanotechnology to plaque biological components. Studies of events and materials with length scales below 100 nm dominate official definitions of nanotechnology. Nanotechnology was originally associated with the miniaturization of semiconductor materials but has now been adapted to provide novel solutions to the clinical management of disease, giving rise to the term nanomedicine.

Targeted drug delivery by nanotechnology has been successfully used for the systemic delivery of a variety of drug molecules, depicting an enhancement in therapeutic efficacy and mitigation of side effects compared to freely administered drugs. Recent advances have shown the potential of nanomedicine-based treatment strategies for cardiovascular diseases. However, like any strategy, there are limitations on the use of targeted drug delivery by nanoparticles (NPs). Clearance by the immune system before a nanoparticle can reach its target is one of the major hurdles that almost all platforms must overcome.
Risk Factors
Main classical risk factors for atherosclerosis include high LDL cholesterol level, diabetes mellitus, cigarette smoking, hypertension, insulin resistance, obesity, inactive lifestyle, and genetic abnormalities (Figure 1).

Pathophysiology of Atherosclerosis
Atherosclerosis is often characterized by the build-up of fatty deposits and the formation of plaques in the walls of large and medium arteries, followed by a strong immunological response to the fatty deposit accumulation. CVD risk factors promote atherogenesis by damaging the endothelium. Healthy endothelial cells release nitric oxide (NO) to induce vasodilation in response to stimulants such as platelet aggregation. When the release of NO is reduced, endothelial dysfunction ensues. The disease is initiated by the activation of the endothelium/endothelial cell (EC) dysfunction (Figure 2). Lipids in the blood, LDL, VLDL bind to endothelial cells and oxidize in the subendothelial space. This trapped LDL can then become oxidized to form oxidized LDL (oxLDL). This triggers a chronic inflammatory response. This involves the release of chemokines, such as monocyte chemotactic protein-1 (MCP-1), and inflammatory cytokines that recruit predominantly circulating monocytes and T-cells to the site of activation. According to the modified ‘response to injury’ hypothesis, recruited monocytes adhere to the activated endothelium before migrating into the intima. Monocytes initially ‘roll’ and adhere to endothelial adhesion markers, such as P- and E-selectins, through binding of surface fucosylated and sialylated carbohydrate ligands. In addition, the ECs express adhesion proteins, such as intercellular adhesion molecule-1 (ICAM1) and vascular CAM1 (VCAM1), that participate in the recruitment of immune cells facilitating monocyte migration through the endothelium. Monocyte migration is further aided by endothelial-expressed chemokines and cytokines, such as MCP-1, macrophage colony-stimulating factor (M-CSF), interleukin-8 (IL-8), and tumor necrosis factor-a (TNF-a), and by platelet endothelial cell adhesion molecule-1 and junctional adhesion molecule-A at cell-cell junctions to mediate trans-endothelial diapedesis. Once through the endothelium, monocytes can differentiate into macrophages, which, amongst other things, ingest trapped native and modified LDL or lipoprotein remnants within the intima and become cholesterol-rich foam cells. These accumulate to create fatty streaks that subsequently mature into more complex atheromas.
fatty streaks into more advanced plaques produces lesions that are usually covered with a fibrous cap composed of vascular smooth muscle cells (VSMC) and extracellular matrix (ECM) molecules. As the lesion progresses, calcification may then occur through mechanisms similar to those in bone formation. In addition to proliferation, cell death (including apoptosis) commonly occurs in the established atherosclerotic lesion. The death of lipid-laden macrophages can lead to extracellular deposition of tissue factor (TF), some in particulate form. The extracellular lipid that accumulates in the intima can coalesce and form the classic, lipid-rich necrotic core of the atherosclerotic plaque. The stability of the plaque is dependent on a balance between ECM synthesis and breakdown. If this balance is lost then the stability of the plaque is jeopardized and the risk of rupture and thrombosis is increased. VSMC are the main producers of the ECM components so their proliferation and migration are very important in maintaining plaque stability. The level of VSMC apoptosis also plays a key role in determining plaque stability due to the release of ECM degrading enzymes by apoptotic cells that can be highly detrimental to the integrity of the fibrous cap.

Figure 2: Pathophysiology of atherosclerosis

Nanotechnology and Nanomedicine

In nanotechnology, the synthesis and development of different nanomaterials are included. To be considered a nanoparticle, an item must be between 1 and 100 nanometers in size. Several fields have been included with nanotechnology, including biology; engineering; and technology. Pharmaceutical sciences and technology use nanomaterials extensively. Drug delivery, diagnostic imaging, and biosensors are a few additional fields where nanotechnology is used extensively. Nanomedicine is the prevalent term for these devices. These materials (1 μm in size) are utilized in therapy, monitoring, and diagnostic procedures.

To produce observable signals, nanoparticles have certain size-dependent characteristics, notably in terms of optical and magnetic parameters. The nanometer scale is interesting in biological systems. Many proteins are ~10's of nm in size. Since structures can be accurately designed on the nanometer scale they can be incorporated into biological systems, due to the similar size scales. Biological systems are complex, with synthesis, structure, and function all rarely understood in detail. The ability to rationally design structures of the same size as biological molecules generate the ability to probe and modify biological systems. Furthermore, biological systems are used to build up nanomaterials of specific shapes and functions. Nanostructures are being used as drug delivery agents, labeling agents, sensors, and to enhance electromagnetic fields.

In addition to having high specific surface areas, nanoparticles also have unique adsorption properties due to different distributions of reactive surface sites and disordered surface regions. NP optimization with surface modifications is required to design a more effective and successful therapeutic. Different possible modifications have been investigated for passive or active drug targeting. For example, coating NP with hydrophobic molecules, such as PEG, poloxamer, poloxamine, and polysorbate 80 (Tween 80), is associated with prolonged circulation time and reduced phagocytosis.

Various pharmaceutical nanotechnology-based systems which can be termed Nanopharmaceuticals like polymeric nanoparticles, magnetic nanoparticles, liposomes, carbon nanotubes, quantum dots, dendrimers, metallic nanoparticles, etc. have brought about revolutionary
changes in drug delivery as well as the total medical service system.\(^\text{36}\)

Nanomaterials can be broadly classified into two categories based on their chemistry: inorganic (non-carbon) and organic (hydrocarbon) nanomaterials. Due to the very large number of studies and versatile applications, carbon-based nanomaterials (such as graphene, carbon nanotubes, and fullerenes) are considered as a separate class of nanomaterials with a wide range of morphologies.\(^\text{37}\)

**Figure 3: Classification of nanoparticles \(^\text{37}\)**

- **Inorganic nanoparticles** – Nanomaterials that consist of only one element are defined as metal NPs. They can exist as individual atoms or clusters of many atoms. Nanoparticles with a variety of metal cores, each with their own optical, electronic, catalytic, or magnetic properties that can enable a variety of optical and electronic applications. Palladium and platinum nanoparticles generally find use as supported catalysts, and Pd and Pt NPs have been shown to catalyze a variety of C-C bond forming reactions.\(^\text{38,39}\)

Silver nanoparticles actively dissolve under physiological conditions to give silver ions, the active ingredient in potent antimicrobials.\(^\text{40}\) Gold NPs (AuNPs) have unique properties, such as size- and shape-dependent optical and electronic features, a high surface area to volume ratio, and surfaces that can be readily modified with ligands containing functional groups which exhibit affinity for gold surfaces. The use of DNA-AuNPs for genetic regulation or amine-functionalized conjugates for drug delivery has dignified that toxicity is lower than polymer delivery systems.\(^\text{41}\)

- **Organic nanoparticles** – Liposomes, micelles, ferritin, dendrimers, hybrid molecules, and compact polymeric NPs are commonly categorized as organic NPs. These particles are considered environmentally friendly as they are biodegradable and non-toxic. Materials with hollow cores (e.g., liposomes and micelles) are sensitive to electromagnetic (light) and thermal radiation (heat) energy. Most of these NPs are ideal for drug delivery applications due to their high stability, biocompatibility, surface morphology, drug-carrying capacity, and delivery efficiency.\(^\text{42}\)

**Applications of nanoparticles**

- The conventional ultraviolet (UV) protection sunscreen lacks long-term stability during usage. The sunscreen including nanoparticles such as titanium dioxide provides numerous advantages. The UV protection property of titanium oxide and zinc oxide nanoparticles as they are transparent to visible light as well as absorb and reflect UV rays found their way to be used in some sunscreens. Some lipsticks use iron oxide nanoparticles as a pigment.\(^\text{43}\)

- Nanoparticles contain a high surface area that offers higher catalytic activity. Due to their extremely large surface-to-volume ratio, the nanoparticles function as an efficient catalyst in the production of chemicals.\(^\text{44}\) Palladium and platinum nanoparticles generally find use as supported catalysts, and Pd and Pt NPs have been shown to catalyze a variety of C-C bond forming reactions. The organometallic catalysis community
has recently recognized that some of their molecular catalysts may function as precursors to active Pt or Pd nanoparticle catalysts.\textsuperscript{38,39}

- As silver nanoparticles have broad-spectrum antimicrobial activity against several pathogens, they are increasingly incorporated into various matrices to extend their utility in materials and biomedical applications.\textsuperscript{40} They are used as additives in health-related products such as bandages, catheters, and other materials to prevent infection, particularly during the healing of wounds and burns.\textsuperscript{45}

Nanotechnology has gained wide attention where more investment is made for research and development by top institutions, industries, and organizations. Nanotechnology has been established to be an advanced field of science where extensive research is carried out to implement the technology.\textsuperscript{45}

In addition to improving therapeutic and diagnostic agents' efficacy, nanomedicine offers the ability to reduce patients' exposure to toxicity and severe side effects. It has been shown that peptides intended to target cells such as endothelial cells, macrophages, and smooth muscle cells (SMCs) and platelets, as well as atheromatous plaque components including collagen and fibrin can effectively cure, prevent and diagnose atherosclerosis in recent research.\textsuperscript{46}

**Diagnosis of Atherosclerosis**

**Early Diagnosis**

Imaging methods that allow for the observation and characterization of atheromatous plaques, as well as the monitoring of their development or regression, have made tremendous strides in recent years.\textsuperscript{47}

**Coronary Angiography**

Angiography of the heart has been utilized for more than 25 years as a diagnostic technique for heart disease. An iodinated contrast agent is injected through a catheter inserted at the ostium of the coronary arteries. Heart x-ray fluoroscopic examination shows the contrast agent.\textsuperscript{47}

Using this technique, we can examine the impact of atherosclerosis on the coronary artery lumen and determine if an intervention delays or reverses the course of atherosclerotic disease over time.\textsuperscript{48}

**Intravascular Ultrasound**

Histological composition influences the stability of atherosclerotic plaques. Intravascular ultrasonography (IVUS) provides the imaging of atherosclerotic plaques in vivo, allowing for the diagnosis of susceptible atheroma before rupture.\textsuperscript{49} As well as measuring the size of the coronary lumen, intravascular ultrasonography may also measure the acoustic density of the artery walls and their thickness.\textsuperscript{50}

Coronary angiography cannot detect atherosclerotic plaque, while intracoronary ultrasonography can.\textsuperscript{51}

**Optical Coherence Tomography**

Tomographic intra-arterial imaging at high resolution (10 m) is possible using optical coherence tomography (OCT), which is an optical counterpart of intravascular ultrasound.\textsuperscript{52} Due to OCT's unique capacity to discern micrometer-scale characteristics of atherosclerosis, this novel imaging technique provides an intriguing way to identify features of coronary plaques at risk for rupture.\textsuperscript{53}

Due to the substantially shorter wavelength of the imaging light compared to ultrasound, optical coherence tomography enhances localization of the returning signal origin; hence, OCT delivers much-enhanced resolution.\textsuperscript{54} OCT detects even the earliest stages of intimal thickening, homogeneous thin rim of tissue having a texture similar to fibrous plaque components.\textsuperscript{55} OCT can also be used to identify the major tissue components of fibroatheromas, including fibrous tissue, lipids, and calcium.\textsuperscript{56} Results from intracoronary OCT, have shown an improved capability for characterizing plaque microstructure compared with intravascular ultrasound.\textsuperscript{57}

**Ultrasound**

Even though ultrasound imaging is a safe, quick, and relatively inexpensive way to detect atherosclerosis, its application is primarily limited to the peripheral vasculature and carotid.\textsuperscript{58} This method is extensively used to depict carotid intimal media thickening (IMT) as well as the presence of plaque. IMT indicates the early stage of plaque formation and the appearance of plaque indicates the advanced stage of atherosclerosis.\textsuperscript{59} Every 0.1-mm increase in IMT increases the risk of myocardial infarction by 10% and stroke by 18%.\textsuperscript{60} It has been demonstrated that high-resolution carotid artery flow-limiting stenosis may be accurately detected with high-resolution B-mode and Doppler ultrasonography.\textsuperscript{61} There is a greater temporal and spatial resolution than other imaging modalities when using ultrasound in the therapeutic environment. As a result, transcutaneous ultrasonography can only be used to assess superficial vascular systems.\textsuperscript{62}

**Computed Tomography**

Using computed tomography (CT) as a marker of atherosclerosis, it is possible to define the arterial location and quantify the relative load.\textsuperscript{63} A CT scan allows the imaging of the coronary artery lumen and the identification of coronary artery stenoses. Plaque disruption, on the other hand, was more difficult to detect using a CT scan.\textsuperscript{64,65}

**Magnetic Resonance Imaging (MRI)**

MRI is a noninvasive modality able to evaluate atherosclerotic plaque in any vascular territory.\textsuperscript{66} MRI can differentiate lipid core, fibrous cap, calcifications, intraplaque hemorrhage, normal intima, and adventitia in vivo in human atherosclerotic plaques.\textsuperscript{67} The basic MRI sequence requirements for vessel wall imaging are high spatial resolution, high contrast between different plaque components, and suppression of extrinsic motion, as well
as the signal from flowing blood. MRI has the potential to provide lesion-specific risk assessments. Furthermore, they indicate the importance of both morphological characteristics and plaque composition for assessing risk. The key advantage of MRI is the opportunity to acquire and combine multi-contrast images, both bright blood (such as time-of-flight, TOF) and black blood (such as T1W, T2W, and PDW with blood-flow suppression) to distinguish tissue composition within the atherosclerotic vessel wall. High-resolution contrast weighting MRI has been used for in vivo assessment of atherosclerotic plaques in the human carotids aortic, peripheral, and coronary arterial disease.

**Nanoparticles in diagnosis**

Nanoparticle-based imaging of cardiovascular interventions is still in its developing phase, it has already presented the exciting potential to monitor primary interventional procedures for precise therapeutic delivery, enhance the effectiveness of delivered therapeutics, and monitor therapeutic efficiency after interventions are performed to treat cardiovascular diseases. The application of molecular imaging in assessing vulnerable atherosclerotic plaques is a challenging task since these plaques are highly complex and constantly evolving structures. Consequently, these lesions display numerous molecular targets, expressed either at the endothelial surface or sub-endothelial by cells and the extracellular matrix in the vascular wall. There are recognized six states of plaque development in humans, divided into precursor and advanced types. Precursor lesions (type I, II, and III) are asymptomatic and do not narrow the lumen, whereas advanced lesions (types IV, V, and VI) are hemodynamically and clinically more relevant since they may lead to ischemic complications.

Almost all nanoparticle-based assays depend on the binding of a nanoparticle label or probe to the target biomolecule to create a detectable signal. Table 1 represents the NPs used in diagnostic in atherosclerosis.

### Table 1: Nanoparticles used in diagnostic area

<table>
<thead>
<tr>
<th>AHA Stage</th>
<th>Characteristics</th>
<th>Molecular Target</th>
<th>Nanoparticle</th>
<th>Imaging modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Activated endothelium</td>
<td>VCAM-1 (luminal)</td>
<td>$^{123}$I or $^{99m}$Tc</td>
<td>Nuclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-selectin (luminal)</td>
<td>Magneto-optical Nanoparticles</td>
<td>-Optical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Microbubbles</td>
<td>-Ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Iron oxide particles</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Magneto-fluorescent NPs</td>
<td>-Optical and MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Iron oxide NPs</td>
<td>-MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Microbubbles</td>
<td>-Ultrasound</td>
</tr>
<tr>
<td>II/III</td>
<td>Macrophages/Inflammation</td>
<td>-MMPs (sub-endothelial)</td>
<td>Near-infrared probe</td>
<td>Optical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Cathepsin K (sub-endothelial)</td>
<td>Near-infrared probe</td>
<td>Optical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Macrophage Scavenger Receptor (CD204) (sub-endothelial)</td>
<td>Immunomicelles</td>
<td>-Optical and MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-P2 receptors or adenosine nucleotide receptors (sub-endothelial)</td>
<td>$^{18}$F</td>
<td>-MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Glucose transporters (sub-endothelial)</td>
<td>$^{18}$F</td>
<td>-Nuclear</td>
</tr>
<tr>
<td>III</td>
<td>Apoptosis</td>
<td>-Cell surface-expressed phosphatidylserine (sub-endothelial)</td>
<td>$^{99m}$Tc</td>
<td>Nuclear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Cell surface-expressed phosphatidylserine (sub-endothelial)</td>
<td>Iron oxide NPs</td>
<td>-MRI</td>
</tr>
<tr>
<td>IV</td>
<td>Angiogenesis</td>
<td>-avb3 (luminal)</td>
<td>Paramagnetic NPs</td>
<td>Optical and MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-CD13 (luminal)</td>
<td>Paramagnetic QDs</td>
<td>-MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Vascular Endothelial Growth Factor Receptor 2 (luminal)</td>
<td>-64Cu</td>
<td>-Optical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Vascular Endothelial Growth Factor Receptor (luminal)</td>
<td>Near-infrared probe</td>
<td>-Nuclear</td>
</tr>
</tbody>
</table>

©Copyright protected. Unauthorised republication, reproduction, distribution, dissemination and copying of this document in whole or in part is strictly prohibited.
Treatment
Early Treatment

In addition to ischemic stroke, coronary heart disease, and myocardial infarction, atherosclerosis can also cause peripheral arterial disease.\textsuperscript{75}

**Anti-hypertensive agents**

Coronary artery disease and stroke are linked to high blood pressure, and it is the world's most significant risk factor for mortality.\textsuperscript{76} Anti-hypertensive agents such as verapamil and amlodipine (calcium channel blocker) are considered to be anti-atherogenic. In cells generated from morphologically normal intima, they prevent the atherogenic serum-induced promotion of cell proliferation, protein synthesis, and cholesterol buildup.\textsuperscript{77} In some studies, Propranolol decreases aortic endothelial turnover which prevents atherosclerosis in broad-breasted turkeys.\textsuperscript{78}

**Anti-diabetic agents**

Most antidiabetic drugs have been shown to have anti-atherosclerotic effects in addition to reducing blood sugar. Metformin has been considered as the first line of treatment for T2DM in many countries (table 2).\textsuperscript{79} Inhibition of the PKC pathway by metformin lowers oxidative stress and can also delay plaque development.\textsuperscript{80} Increased oxidative stress is very common in diabetic patients and leads to the oxLDL mainly responsible for atherosclerosis. In vitro, Gliclazide prevents LDL oxidation, and it lowers the plasma lipid peroxide levels in patients with type II diabetes.\textsuperscript{81}

**Figure 4: Treatment of Atherosclerosis**\textsuperscript{75}
Anti-atherosclerotic actions have also been demonstrated for thiazolidinediones. The thiazolidinedione derivatives, pioglitazone, and rosiglitazone, are synthetic ligands for peroxisome proliferative-activated receptor (PPARγ) which improve insulin sensitivity. In particular pioglitazone has been shown to improve endothelial function in diabetes. It was observed pioglitazone improves shear-stress induced flow-mediated vasodilation of brachial artery in patients with type II diabetes with no effect on endothelium-independent vasodilation. In addition, pioglitazone has also been shown to reduce LOX-1 as well as VCAM expression which can potentially prevent plaque formation. Thiazolidinediones are the most widely studied agents and it appears that they have the potential to delay the progress of atherosclerosis.

Statins

Recent advances in the management of hypercholesterolemia are primarily due to the development of 3-hydroxy-3- methylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statins. HMG CoA reductase is an enzyme responsible for cholesterol formation in the liver. Statin therapy is associated with regression of coronary atherosclerosis when LDL-C is substantially reduced and HDL-C is increased by more than 7.5%. Statin benefits are derived from both reductions in atherogenic lipoprotein levels and increases in HDL-C.

Antiplatelet agents

Negative modulation of platelet adhesion and aggregation is exerted by a variety of mechanisms, including endothelium-derived prostacyclin (PGI2), nitric oxide, CD39/ecto-ADPase, and platelet endothelial cell adhesion molecule-1 (PECAM-1). Oral antiplatelet agents—particularly aspirin and the thienopyridine clopidogrel and ticlopidine—constitute a cornerstone of therapy for vascular disease given the integral role of platelets in the progression of atherosclerosis and acute clinical events including myocardial infarction, ischaemic stroke, and sudden death. Aspirin inhibits cyclo-oxygenase to reduce the production of the platelet activator thromboxane A2. The thienopyridines inhibit multiple pro-aggregatory actions of the platelet agonist adenosine-50'-diphosphate (ADP) by blocking the P2Y12 platelet ADP receptor.

Angioplasty

Atherosclerotic stenoses have been successfully treated with percutaneous transluminal angioplasty (PTA) in the coronary and peripheral circulations. PTA results in wider patency of the infarct-related coronary vessel and that immediate PTA is associated with low rates of recurrent ischemia and death. The mechanism by which transluminal angioplasty reduces luminal narrowing in humans remains largely undefined. Earlier clinical and pathological studies have suggested that redistribution or compression of the intramural lipid within the plaque might occur. When eccentric, fibrotic lesions are present, balloon dilatation results in stretching of the non-atherosclerotic media and aneurysm formation. Once the muscle fibers are stretched, as demonstrated by the corkscrew deformity of their nuclei, the artery no longer resists its original size following deflation of the balloon, and a permanent widening occurs.

Bypass surgery

Aortocoronaryvein bypass surgery for obstructive coronary artery disease is an effective means of reducing or eliminating symptoms of myocardial ischemia. Several previous studies have suggested, however, that although successful bypass surgery improved coronary flow reserve in the perfusion field of the bypass graft, it does not restore it to normal levels.

Treatment by Nanoparticles

Lipoprotein mediated treatment

Intravenous administration of the PCSK9siRNA loaded nanoparticles into different animal models including mouse, rat, and nonhuman primate decreased levels of PCSK9 transcripts in the liver. These nanoparticles also lowered plasma concentrations of PCSK9 protein and LDL cholesterol but had little effect on plasma concentrations of HDL cholesterol and triglyceride. HDL takes up cholesterol from peripheral tissues such as the vessel macrophages back to the liver and then excreted from the body which is referred to as reverse cholesterol transport (RCT). Synthetic HDL enables targeted delivery of LXR agonist to induce atherosclerosis regression through enhancing two steps. Firstly, an increase of the cholesterol acceptor-HDL and secondly, induction of cholesterol efflux in atherosclerotic plaques by LXR agonist.

This multifunctional nanocarrier containing LXR agonist...
selectively activates LXR targets genes in atherosclerotic plaques, without damaging the liver. 99

**Anti-inflammatory treatment**

Dexamethasone (DXM), an anti-inflammatory steroid drug, can inhibit atherosclerosis development via decreasing intimal macrophage recruitment and foam cell formation.100 Despite that, long-term administration of dexamethasone has side effects including weight gain, depression, and hypertension. DXM-loaded liposomes are acquired with different particle sizes (70, 200, 500 nm). In comparison to free DXM and liposomes remarkably decrease aortic cholesterol content, which correlated with increased aortic uptake of DXM.101

Glucocorticoid, an anti-inflammatory steroid drug show atherosclerosis treatment but is not used clinically due to certain side effects and poor pharmacokinetic profile. Studies show a significant decrease in inflammatory response on day 2 and lasted for 5 days in the rabbit model after injecting glucocorticoid-loaded liposomes at a dose of 15mg/kg.102

**CONCLUSION**

While understanding the molecular etiology of atherosclerotic disease develops, the development of nanoparticle medicines for the detection and therapy of the illness will continue to progress. In comparison to small-molecule drugs, nanoparticles provide enhanced bioavailability and the potential to target processes.

When it comes to the management of cardiovascular disease in general, nanomedicine shows promise as a kind of customized medicine, particularly when it comes to target-specific treatment and imaging of atherosclerotic illness. We will be able to prevent and cure atherosclerosis by discovering novel molecular targets, improving our knowledge of atherosclerosis’ pathogenesis, and advancing nanoparticle manufacturing processes and imaging technology. For the treatment of CVDs, however, only a few nanomedicine-based methods have been authorized. However, despite the obstacles, past research has shown that nanomedicine has enormous potential as one of the most promising methods for treating cardiovascular diseases. As a consequence of a complete understanding of CVD pathophysiology, novel biomarkers and therapeutic targets may be discovered, offering fresh insight for future nanomedicine innovation. In addition to gene editing and chimeric antigen receptor T cell methods, nanomedicine increases the spectrum of applications for these technologies, demonstrating the delicate interplay between nanomedicine and other sophisticated technologies, even mixing them for synergetic results.

**REFERENCES**


51. Ibanez B, Navarro F, Cordoba M, Alberca PM, Farre J. Tako-susbtobrastent left ventricular apical ballooning: is intravascular ultrasound the key to resolve the enigma?. Heart 2005; 91: 102-104.


**Source of Support:** The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Conflict of Interest:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

For any question relates to this article, please reach us at: editor@globalresearchonline.net

New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit_ijpsrr@rediffmail.com