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# Are We Stagnant at Managing Atherosclerosis? A Review on Emergent Therapies in Treating Coronary Artery Disease (CAD)

**Riddhi Machchhar*, Tasfia Tasnim and Carl Hock**

*Department of Osteopathic Medicine, Rowan School of Osteopathic Medicine, Stratford, New Jersey, USA*

## Abstract

Presently, Coronary Artery Disease (CAD) is medically managed to reduce cardiovascular morbidity and mortality, improve ischemic burden and maintain quality of life. Development of underlying atherosclerosis may be prevented via primordial prevention with risk management but once the inflammatory process of plaque formation initiates, there is a lack of therapeutic intervention in reversing this cascade. Conventional therapies include long-term pharmacologic management with aspirin and antiplatelet agents in reducing the risk of thrombosis. Furthermore, surgical management with coronary artery bypass graft and coronary artery stenting have shown efficacy in decreasing mortality, yet the risk of restenosis is relatively high. This paper explores emerging therapies in surgical intervention, the use of nanotechnology, and pharmacological advancements in managing and somewhat reversing atherosclerosis in CAD. Innovation to coronary stenting is brought by the integration of nano-coated metals and biodegradable-polymer drug-eluting stents that have shown optimal efficacy when compared to traditional stent architecture. Similarly, nanotechnology is at the forefront of CAD research with promising reversal of atherosclerosis. It does so by mimicking the intrinsic properties of HDL and targeting lesional macrophages involved in continuous inflammation in a vulnerable plaque. Much more, exploring pharmacological advancement reveals the current development of drug encapsulated cargo-switching nanoparticles and the harnessing of existing anti-inflammatory agents in managing atherosclerosis. Whether these advancements can be practically implemented in managing atherosclerosis or stay as theoretical proposals in literature is up for discussion in the field of cardiology.

**Keywords:** Coronary artery disease (CAD) • Atherosclerosis • Nano-technology

## Introduction

Cardiovascular disease, in particular atherosclerotic coronary artery disease (CAD), is the leading cause of morbidity and mortality in the United States [1]. About 18.2 million adults aged 20 and older have CAD, which is 6.7% of the total population in the United States [2]. It is responsible for killing about 365,914 people in the year 2017 alone [3]. Furthermore, about 2 in 10 deaths from CAD happen in adults less than 65 years old making it a field in great need of advancement and novel therapeutic intervention [3].

Much of novel therapeutic interventions can be derived from the fundamental understanding of how atherosclerotic plaque forms, why certain coronary arteries are more prone to thrombosis than others and what makes a plaque unstable leading to rupture. Through the consensus of multiple investigators, the American Heart Association categorized human coronary lesion morphologies as nonatherosclerotic intimal lesions, progressive atherosclerotic lesions, lesions with acute thrombosis, and complications of hemorrhage and/or thrombus with healing and stabilization [4-6]. To expand, no atherosclerotic precursor lesions can be categorized as an adaptive intimal thickening and intimal xanthoma. In atherosclerotic prone arteries, including the coronary, carotid and iliac arteries, the artery undergoes intimal thickening as part of physiological response to blood flow [7,8]. This physiological change is also witnessed at arterial branch points in younger adults and is a risk factor for future plaques with potential thrombosis [4-8]. In contrast, intimal xanthomas, also known as “fatty streaks”, are collections of infiltrating macrophage foam cells or lipid-laden Smooth Muscle Cells (SMCs) that transiently invade the arterial intima and potentially regress in younger individuals [4-6].

Progressive permanent atherosclerotic lesions primarily begin with pathological intimal thickening composed of SMC remnants within an extracellular matrix (ECM) composed of proteoglycans and type III collagen with an aggregated lipid pool [5,6,9]. Continued intimal growth is enhanced by the apoptosis of SMCs, where the growing intimal lipid pool is found to be in conjunction with foamy macrophages at arterial branch points [5,6]. The direct attraction between the negatively charged sulfate groups present in proteoglycans and the positively charged domains of apolipoprotein B (apoB), facilitated by the activity of lipoprotein lipase, leads to the subendothelial retention of lipids [10,11]. The macrophages present in the lipid pool eventually undergo apoptosis creating an acellular necrotic core called fibroatheroma [5,6].

In an early fibroatheroma, the necrotic core has a decreasing amount of extracellular matrix and an increasing amount of matrix metalloproteinases (MMPs) leading to an expanding lesion and continuous inflammation [12]. On the other hand, in late fibroatheroma, the core is devoid of any extracellular matrix but has more cholesterol clefts, associated with calcification, intraplaque hemorrhage, and surrounding angiogenesis [5,6]. These are harbored within a thick fibrous cap composed of type I and type III collagen. The thick fibrous cap is vulnerable to thinning and potentially ruptures and is believed to be due to ECM degradation facilitated by MMPs and proteases secreted by an overabundance of macrophages [12].

Thin fibrous cap fibroatheroma (TCFA) with a thickness of 55-84 um is synonymous with a vulnerable plaque and is prone to spontaneous rupture [13]. It is characterized by a necrotic core full of apoptotic cellular debris and diseased vascular cells uncleared by phagocytic cells [14]. Upregulation of CD47, a key anti-phagocytic marker, is highly associated with atherosclerosis making them resistant to the physiological process of removal [15]. A widely accepted belief that rupture of a vulnerable fibrous cap takes place at the

***Address for Correspondence:** Riddhi Machchhar, Department of Osteopathic Medicine, Rowan School of Osteopathic Medicine, Stratford, New Jersey, United States, E-mail: machch72@rowan.edu*



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weakest point around the shoulder region, however, atherosclerotic plaque may also rupture in the midline secondary to stress-induced during exertion, such as heavy lifting or shoveling snow [5,6]. Once ruptured, the necrotic core is exposed to the circulating blood, initiating the coagulation cascade and subsequent thrombus formation. The thrombus is later broken down physiologically and the cycle of atherosclerosis continues with progressive inflammation leading to intimal narrowing.

The frequency at which an atherosclerotic plaque ruptures depends on the stability of the fibroatheroma lesion. As previously mentioned TCFAs are indicative of a vulnerable or unstable plaque but that alone is not enough to indicate a predisposition of harm. Unstable or vulnerable plaques must comprise of three qualities: thin cap fibroadenoma (TCFA), pathological intimal thickening, and calcified plaque with the potential to create luminal thrombosis [16,17]. While it is established that the necrotic core of a ruptured TCFA perpetuates the coagulation cascade, the varied presence of cholesterol clefts increases the risk of plaque instability. The number of cholesterol clefts in the necrotic core was significantly greater in the ruptured plaques than in erosion or stable plaques with >75% cross-sectional luminal narrowing [16,17]. The presence of cholesterol clefts defines one aspect of plaque vulnerability, but it is imperative to also evaluate other aspects of plaque character. Areas of intimal thickening, a factor in plaque instability, are most significant in the proximal portions of the major coronary arteries, left anterior, left circumflex and the right [16]. In contrast, sites of <50% diameter of luminal narrowing characterize a stable plaque [16].

The third aspect of an unstable plaque is the presence of calcified nodules. The impact of calcified nodules is intricate as they rarely trigger thrombosis but are notable in victims of sudden coronary death or those afflicted by acute myocardial infarction [16]. Interestingly, while calcification is present in unstable angina, defined as 75% or more artery occlusion, the age of the patient is pertinent when considering risk. The older the population, the more likely a clinician will observe calcifications. In addition, the degree of calcification in women is ten years behind the rate seen in men but tends to equalize by the eighth decade [16].

The pathophysiology and our understanding of coronary artery disease have undergone significant evolution from the concept of cholesterol storage disease to a sequential inflammatory process. Currently, the mainstay interventions for Coronary Artery Disease (CAD) are invasive, such as cardiac catheterization with stenting and coronary artery bypass graft (CABG). Even so, these interventions are not permanent and are prone to re-occlusion. Patients who are not candidates for these interventions are managed pharmacologically with statins and blood thinners, which do not reverse atherosclerosis. This literature review aims to source innovative alternatives and emerging interventions for reversing atherosclerosis and management for CAD; as well as evaluate their importance and implications.

## Health Promotion and Disease Prevention

The traditional approach towards cardiovascular risk assessment is considered as "ABCDE: Assess, Base Risk Estimation, Consider, Develop, Engage[18]." A risk factor assessment can promote primordial or primary prevention of cardiovascular disease (CVD) by providing insight for at-risk patients and encouraging health promotion. Initially, one is assessed for traditional risk factors as defined by the Framingham Heart Study. Age (males ≥ 45 years or females ≥ 55 years), male sex, hypertension (HTN), dyslipidemia, smoking, and diabetes mellitus (DM) are concrete factors from the study which can be adjusted for premature atherosclerotic CVD (ASCVD). Once the traditional factors are accounted for then base risk estimation via population-based risk scores are evaluated. This entails considering a multivariate risk model inclusive of ethnicity, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, and treatment for HTN, DM, and smoking. By comparing risks, an informed conversation regarding individual risk, treatment, and predicted outcomes can be made [18].

An additional layer of risk assessment considers nontraditional risk factors, biomarkers, and non-invasive measures. These nontraditional factors comprise of Metabolic Syndrome (MetS), inflammatory markers, autoimmune disease (like Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), systemic sclerosis), Humane Immunodeficiency Virus (HIV) status, gestational syndromes, extensive comorbidities, psychosocial stressors, and social determinants. MetS, in the absence of DM, confers an increased ASCVD risk that is underrecognized and often not appreciated in an initial screening. Another unique aspect in a patient, the presence of autoimmune disease, can have an increased impact on cardiovascular risk in young to middle-aged females. A detected HIV infection can accelerate the effect of CV risk factors; whereas, pregnant females with either or both gestational DM and gestational HTN have an increased possibility of developing adverse CV risk factors after birth. As expected, the presence of comorbid conditions can exacerbate risk factors in a cardiovascular health profile within older individuals. As might be expected, certain social determinants of health like a lower socioeconomic status and inequity can impact CV risk; and interestingly, additional aspects like major depression after a myocardial infarction (MI) can increase mortality and the possibility of future negative CV events [18].

Traditional and nontraditional risk factors in cardiovascular disease can be addressed with primordial prevention or the prevention of CV risk before the onset of CV disease. If aspects of CVD are present, defined as subclinical atherosclerotic disease with peripheral, carotid, or coronary atherosclerosis, then primary prevention can be initiated. This consists of preventing the precipitation of disease and halting adverse CV events. Secondary prevention, the prevention of the signs and symptoms of disease, apply to appreciate clinical disease like MI, CVA, PAD, heart failure, and recurrent events. To appropriately assess the level of prevention, risk reassessment and reclassification are continuously being modified to decrease the variability of the standard algorithms.

Currently, the C-statistic is the Concordance statistic which defines the Area-Under-Curve or AUC and classifies outcomes. The C-statistic helps clarify future cardiovascular adverse events from nonevents and can help discriminate between the results of different risk assessment tools and screenings. Unfortunately, the C-statistic is limited in supplying the probability of when an adverse event would occur relative to the stratified risk assessment models. In addition, risk reclassification is composed of the net classification improvement (NRI) index and the Integrative Discrimination Index (IDI). The NRI indicates the quantity of reclassification occurring that is statistically significant, whereas the IDI determines how far subjects move on a continuum of predicted risk. When applying NRI to the ASCVD risk score through the investigation of novel markers of subclinical atherosclerosis, the potential enhancement in risk assessment can be demonstrated [18].

Potential assets for CV risk assessment being evaluated are: high-sensitivity CRP for subclinical systemic inflammation; Lipoprotein(a) as a proinflammatory, proatherogenic mark of genetic CVD risk; Apolipoprotein B to calculate a collective atherogenic burden; HDL-C and HDL-C functionality to evaluate a relationship between HDL-C levels and adverse CV events; an Ankle-Brachial Index (ABI) to detect possible PAD, and a Coronary Artery Classification (CAC) score to reveal the effects of varying severity of the coronary calcium burden. While the improvements and evolutions of ASCVD risk are being explored; it is imperative to pursue and advocate for good CV health from the primordial and primary stages. Correspondingly, innovations to treatment are also being forged with improved diagnostics, pharmacotherapy, stenting, and innovational strides with nanotechnology.

## Current Diagnosis and Treatment of CAD

Clinical assessment of patients with symptomatic chest pain begins with achieving a baseline EKG and calculating the pretest probability of CAD, which takes into consideration the patient's age, sex, and type of chest pain [19]. Patients with a very low pretest probability of CAD (<5%) do not require any further diagnostic testing, whereas a low pretest probability of 5%-10% endorses the need for cardiac stress testing [19,20]. An intermediate pretest probability of 10-90% indicates cardiac stress testing or, alternatively, coronary

CT angiography [19,21,22]. A high pretest probability of >90% warrants invasive coronary angiography along with cardiac stress testing and non-stress cardiac imaging [19,21,22]. Once CAD has been diagnosed, the goal of treatment is to reduce cardiovascular morbidity and mortality, improve ischemic burden and maintain quality of life [19,23]. This is achieved through pharmacological management in all patients with aspirin, antiplatelets, lipid-lowering agents, and antianginal medications [19,23]. Unfortunately, there are no anti-atherosclerotic agents to stop or reverse the progression of vascular intimal narrowing at present, indicating a need for advancement in the medical management of CAD. In a select number of patients, mechanical revascularization with Percutaneous Coronary Intervention (PCI) with drug-eluting stents (DES) and coronary artery bypass grafting (CABG) have shown to improve mortality [24]. In the SYNTAX study evaluating 1800 patients with multivessel CAD undergoing revascularization with either PCI with DES or CABG, rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group with an increased rate of repeat revascularization [24-26]. The higher number of adverse events in the PCI group was largely due to repeat revascularization secondary to the faster rate of restenosis even with DES and dual antiplatelet therapy [20]. In the SYNTAX II study, an improved approach to percutaneous interventions in multivessel CAD showed no significant difference in major adverse outcomes when compared to patients with CABG [27]. Similarly, after 5 years of follow-up, a meta-analysis did not show any significant difference in rates of survival between the CABG and PCI groups in patients with left main coronary artery disease with low anatomical complexity [28].

## Limitations to Current CAD Therapies

Conventional pharmacological management of CAD with anti-platelet therapies, including aspirin and clopidogrel, is not devoid of limitations. Aspirin, a nonselective irreversible cyclooxygenase inhibitor, is known for hypersensitivity, gastrointestinal adverse effects, and bleeding in certain patients [29]. Similarly, clopidogrel, a P2Y12 receptor inhibitor that blocks ADP mediated expression of GpIIb/IIIa necessary for platelet aggregation, is known for increased risk of bleeding, adverse drug interactions and prolonged duration of action that requires early cessation of the drug prior to any surgical intervention [29]. Furthermore, clopidogrel is activated by hepatic metabolism and can vary in efficacy due to genetic polymorphisms in different patients [29]. Despite the role of conventional therapies in lowering cardiovascular mortality, the adverse effects and the relatively high risk of myocardial infarction in CAD prove the need for emergent agents in the management of atherosclerosis [29].

Similarly, over the last 40 years, percutaneous coronary angiography has undergone major advancements to limit cardiovascular adverse outcomes. Introduction of first-generation drug-eluting stents (DES), as opposed to bare metal stents, demonstrated improved efficacy with a dramatic reduction in in-stent restenosis and target lesion revascularization [30]. However, major safety concerns emerged with first-generation DES in clinical practice as a result of the high incidences of death, myocardial infarction (MI), and repeat revascularization associated with stent thrombosis [30]. More so, very late stent thrombosis continues to progress even up to 10 years after intervention [30]. To overcome these barriers, improvements in stent architecture including nano-technology and biodegradable polymer-based DES have come under exploration [30]. Furthermore, CABG has shown relative optimal efficacy against pharmacotherapy and percutaneous coronary intervention. Yet the cost of undergoing CABG without postoperative complications was approximately $36,000 in the year 2015 alone and has continued to rise since then [31]. When comorbidities along with postoperative complications existed, the cost increased exponentially demonstrating a need for better cost containment [31].

The complexity of atherosclerosis in the context of coronary artery disease makes management a dynamic process, where the limitations to current management add to the variability. Thus, emergent therapies are long overdue in the field of cardiovascular health.

## Emergent Therapies

### Coronary stents

Percutaneous Coronary Intervention (PCI) has evolved from balloon angioplasty to bare-metal stent (BMS) and drug-eluting stents (DES) [32]. Compared to BMS, drug-eluting stents release anti-proliferative medication to prevent restenting. DES uses medications such as Sirolimus and Paclitaxel but have gone through three generations of stent coating-material modifications for the most optimized utility [33]. Unfortunately, re-endothelization has been observed with current DES technology, despite the advancements made, due to platelet activation and late thrombotic events [33]. While these complications are rare, they prove to be acute, unpredictable, and dangerous.

Currently, improvements to stenting, through the therapeutic potential of nanotechnology, are being tested. “Nanotechnology allows for efficient modulation of surface roughness, chemistry, feature size, drug/biologics loading, to attain the desired biological response [33].” The future of intervention could include nano-structures, particles, and fibers, with or without the use of drugs/biologics. A major strength in these innovations is that nanotechnology is preferable in size and has the potential to avoid microinsults to the vasculature [33]. The major nanotechnology applications tested are nanoscale architectures on stents or the nano-thin film coating on medically relevant metals such as titanium dioxide, and nano-thin films combined with drugs/biologics [33]. In addition, nanofibrous surfaces and nanoparticulate systems are also being evaluated with the goal to include necessary aspects to move these innovations into clinical trials.

Stent design and architecture are constantly undergoing innovations by building strong endothelial barriers to decrease neoatherosclerosis. This is achieved efficiently by biodegradable-polymer DES and polymer-free DES, which allow superior endothelial healing by a controlled presence of drugs within the arterial wall [34]. Neoatherosclerosis occurs due to impairment of endothelial function from exposure to drugs containing mTOR inhibitors [34]. As such, biodegradable-polymer DES is superior as the polymer is eventually degraded, resulting in a diminishing level of mTOR inhibitor within the arterial wall [34]. This ensures adequate healing and faster return of endothelial function with a lower probability of neoatherosclerosis compared to permanent DES. The superior efficacy and safety of biodegradable-polymer DES were demonstrated in a 10-year study comparing DES with different polymer coatings [35]. Neoatherosclerosis is also reduced by polymer-free DES, which includes circumferential drug coating with a bare lumen. Although this has shown decreased neoatherosclerosis and improved endothelial healing, the bare lumen increases the potential for acute thrombosis [35]. This risk factor decreases significantly with the use of highly fluorinated polymer on stents that reduce platelet adhesion and thrombosis [35]. Yet, continued work is still needed on the architecture, thickness, and coating of stents to better improve outcomes in the management of atherosclerosis. Furthermore, these innovations must move beyond in vitro and in vivo pre-clinical studies to achieve validation through clinical trials.

### Nanotechnology

With the understanding of inflammation as the underlying cause of atherosclerosis, a great number of studies have now pivoted from traditional lipid-lowering agents to targeted anti-inflammatory molecules with the hope of reversing atherosclerosis. Of note, Varespladib, an inhibitor of secretory phospholipase A2 (sPLA2), which interact with LDL particles and modify them into more atherogenic moieties, showed promising results ex vivo by reducing monocyte chemotaxis and oxidation of lipids with subsequent reduction in necrotic core [36,37]. In preclinical pig models, it reduced coronary atherosclerosis primarily by reducing necrotic core volume in addition to stabilization of existing plaque [36]. However, these findings became futile as Phase III clinical trials showed no change in overall plaque volume reduction and an increase in coronary adverse events [36]. Yet, Darapladib, an inhibitor of lipoprotein-associated phospholipase A2 (LP-PLA2), is now being tested in Phase III clinical trial of two large cardiovascular outcome studies — STABILITY and SOLID-TIMI 52 — which will investigate the effect of darapladib on reducing coronary atherosclerosis and cardiovascular mortality [38].

Considering the increased risk of adverse events with generalized anti-inflammatory agents, other emerging therapies have focused on re-priming necrotic core macrophages to induce efferocytosis of diseased vascular cells and reduce atherosclerotic burden. When cells turn over, the apoptotic debris is cleared physiologically by lesional macrophages by recognizing efferocytic receptors [15,39]. To balance the action of clearance, CD47, a ligand for the signal regulatory protein-α (SIRPα) on macrophages that activates the Src homology 2 domain-containing phosphatase-1 (SHP-1) to mediate intracellular signaling for suppressing phagocytic function, is expressed to an appropriate target [15,39]. However, like cancer cells, atherosclerotic plaque in coronary arteries has been shown to upregulate higher numbers of CD47 ligands impairing the removal of cellular debris and fueling the cycle of inflammation in an unstable plaque [39]. Targeted anti-CD47 antibodies showed promising results in *in vivo* mouse models, with marked reduction of apoptotic debris in the necrotic core and a decreased volume of atherosclerotic plaque burden [15]. Unfortunately, anti-CD47 antibodies also upregulate the Fc receptor-mediated off-target removal of red blood cells in the spleen, leading to anemia and potentially exacerbating ischemic burden in patients with atherosclerosis [40,41]. Currently, a breakthrough anti-CD47 antibody, magrolimab is undergoing Phase III clinical trials to determine its efficacy in treating malignancies such as acute myeloid leukemia and advanced colorectal cancer [42,43]. Yet, its benefit in reducing atherosclerotic burden in carotid arteries with the potential to reduce cardiovascular mortality is continued to be proven in retrospective studies with patients undergoing treatment with magrolimab [44].

The off-target removal of RBCs with exacerbation of ischemic burden is a significant concern, but can it be overcome by directing anti-CD47 antibodies to the atherosclerotic lesion of choice? Indeed, precision-engineered nanoparticles have opened the doors to a new generation of atherosclerotic management. A system developed using polyethylene glycol-functionalized single walled carbon-nanotube (SWNTs) and loaded with a fluorescent probe Cy5.5 and a small-molecule inhibitor of CD47's downstream effector molecule, SHP-1, has shown to preferentially accumulate within Ly-6Chi inflammatory monocytes. Ly-6Chi monocytes are particularly important as they are recruited to the diseased artery, where they differentiate into lesional macrophages [45,46]. In two independent murine models, accelerated atherosclerosis and chronic atherosclerosis, treatment with SWNTs showed increased efferocytosis, reduced necrotic core, and reduced accumulation of apoptotic bodies [39]. Furthermore, in vivo PET/CT imaging proved the subsequent reduction of inflammation in mice treated with SWNTs [39]. Unlike direct CD47 antibodies resulting in anemia, targeted nanotechnology proved superior in its remarkable safety profile. In vivo studies showed a slight decrease in platelet count without any difference in bleeding events between the treatment and placebo groups [39]. Even so, there was no effect on the overall leukocyte or neutrophil count and no changes in infectious events were observed [39]. In fact, there was an overall decrease in C-reactive protein, an indicator of inflammation and cardiovascular risk [39].

Expanding on the efficacy of targeted therapy, other studies have focused on biomimetic high density lipoprotein (HDL) as a natural nanoparticle to harness the intrinsic affinity towards lesional macrophages. HDL is the smallest particle in the lipoprotein family, consisting of a hydrophobic core encapsulated by a monolayer of amphiphilic phospholipids and apolipoproteins (ApoA-I and ApoA-II) [47]. Physiologically, HDL accumulates within atherosclerotic plaque and interacts with ATP-binding cassette transporters A1 (ABCA1) and G1 (ABCG1) and the scavenger receptor B1 (SR-B1) on lesional macrophages, to initiate reverse cholesterol transport [48,49]. With this cholesterol removal property, HDL is known to remove lipids from macrophages and recycle them back to the liver [50]. In addition, native HDL stands up to its anti-inflammatory properties by increasing nitric oxide production by endothelial cells [51,52]. Moreover, HDL's intrinsic properties make it suitable for diagnostic and therapeutic processes, making it a focal point of replication. Man-made HDLs, known as reconstituted HDLs (rHDL), are synthesized through the utilization of microfluidic technologies such as emulsion, diffusion, and mixing [53]. Microfluidic formulation processes offer effective control of the characteristics of the nanoparticles and enable them to be created in bulk production [53]. However, studies reveal toxic accumulation of rHDLs in the liver, while compromising reverse cholesterol transport in macrophages necessary for targeting atherosclerosis [53]. To overcome the adverse outcome, a hybrid polymer/HDL nanoparticle composed of a lipid/apolipoprotein coating that encapsulates a poly(lactic-*co*-glycolic acid) (PLGA) core was developed [54]. This novel HDL-like nanoparticle (PLGA–HDL) imitates natural HDL characteristics, including selective uptake by macrophages and a good cholesterol efflux capacity, combined with a typical PLGA nanoparticle slow release profile [55]. To assess this extensive characterization of PLGA-HDL, cholesterol efflux assays were performed in human macrophage-like THP-1 cells comparing native HDL with PLGA-HDL, rHDL, and bovine serum albumin (BSA) as control [55]. Cholesterol efflux of approximately 13% was observed in PLGA-HDL cell lines as opposed to more than 15% cholesterol efflux in cell lines treated with rHDL [55]. Although this considerable amount of cholesterol efflux observed in PLGA-HDL cell lines is promising, it is still lower than what was observed in cell lines treated with native HDL. This could be attributed to the smaller PLGA core, which limits the amount of cholesterol for uptake. However, no particle-related cytotoxicity was observed after 24-hour incubation with macrophage, hepatocyte, smooth muscle, and pancreatic cell lines [55]. Moreover, ex-vivo studies in ApoE knockout mice prone to atherosclerosis treated with PLGA-HDL nanoparticles show selective colocalization within macrophages primarily located along the aorta and the aortic root [55]. This localization in sites primarily involved in atherosclerosis in disease models advocate that PLGA-HDL nanoparticles target atherosclerotic plaques and preferentially accumulate in plaque macrophages, making them a versatile modality for therapeutic and diagnostic intervention [55,56]. Yet, such promising results are only limited to laboratory success and have not entered the realm of clinical studies to date.

## Pharmacotherapy

Advancement in drug delivery holds promising outcomes in targeted therapy. Statins have been the mainstay treatment for cardiovascular risk reduction and prevention. It lowers serum cholesterol by blocking HMG-CoA reductase in hepatocytes and helps with plaque regression within atherosclerotic lesions [57]. In addition to statins, management of comorbidities that affect ASCVD like hypertension, obesity, and diabetes is important.

Innovations to pharmacotherapies have recently been explored with the assistance of nanoparticles to see whether the inflammatory process of atherosclerosis can be halted or minimized. As previously mentioned, fatty deposits of cholesterol trigger macrophages and lead to an adverse cascade of arterial damage. Current treatments cannot reverse the presence of fatty streaks or plaques and the inflammatory markers they attract but a novel therapy is being evaluated. Cargo-switching nanoparticles (CSNP) is a pharmacotherapy currently under observation for its potential to bind cholesterol and apply anti-inflammatory intervention in the plaque microenvironment [58]. The core of CSNP has an inner-core of self-assembled methyl-β-cyclodextrin (cyclodextrin) and simvastatin (statin), and an outer-covering of phospholipids [58]. Therefore, CSNP becomes a homogenized nanoparticle structure with the ability to cargo-switch or have interchanging connections between cyclodextrin, statin, and cholesterol.

Therefore, when cholesterol interacts with a higher affinity to the cyclodextrin within CSNP, a cyclodextrin-cholesterol complex forms, allowing statin to scavenge for and attack cholesterol in the plaque microenvironment. In mouse models of atherosclerosis, systemically injected CSNP targets atherosclerotic plaques and reduces plaque content of cholesterol and macrophages, which synergistically leads to effective prevention of atherogenesis and regression of established plaques [58]. These findings suggest that CSNP provides a therapeutic platform for interfacing with cholesterol-associated inflammatory diseases such as atherosclerosis [58]. During these mouse model studies it was observed that intracellular and extracellular scavenging of cholesterol by CSNP was successful despite its negatively charged surface. The homogenized, lipid-coated, nanotechnology therapy was able to enter macrophages and dissolve intracellular Cholesterol Crystals (CC) and helped provide details regarding an effective-dose and time-dependent dissolution of CC [58].

Furthermore, macrophages with and without intracellular cholesterol were used to see if lipid-laden macrophages affect CSNP's onset of action. It

was found that macrophages injected with low-density lipoprotein (LDL) were susceptible to CSNP; also observable was CSNP activity was negligible in lipid-laden macrophages in which lipopolysaccharide (LPS) became activated as lysosomal degradation was already in effect [58]. In addition, inflammatory processes were evaluated by the use of LPS for anti-inflammation and CC for inflammation. The release of MCP-1, TNF-a, and IL-1β indicate an inflammatory process. CSNP resulted in a significant decrease in the secretion of MCP-1, TNF-a, and IL-1β indicating CSNP uses inclusion complex statin to reduce an activated macrophages' inflammatory response and inhibit cholesterol-mediated inflammation via cyclodextrin [59]. Antiproliferation was evaluated in a dose-dependent manner in which CNSP inhibited macrophage proliferation similarly to statins and at high doses, hindering their viability [59].

CSNP also demonstrated that it could synergistically work to improve the pharmacokinetics of encapsulated drugs, like statins and free cyclodextrin. The mouse models reflected CSNP accumulated in the liver, spleen, and Left Carotid Artery (LCA); exerting significant dissolution of cholesterol within plaques and further exerting an antiatherogenic profile [58]. In fact, in a ligation model, early treatment with CSNP at days 2, 5, 8, and 11 post-ligation reflected stunted atherogenesis. More importantly, especially in established disease, a reversal of plaque formation by this novel core-shell structured nanotechnology therapy was researched. In mice given a high-fat diet and normal diet, it was seen that normal diet mice experienced a decrease in systemic cholesterol level but CSNP therapy was nonsignificant in both groups [59]. Instead, it was further established that diet has an integral role in systemic plasma cholesterol. Likewise, CSNP seemed to have a better therapeutic potential for localized areas of plaque formation. For example, CSNP can augment improved diet because both mice models indicated an improvement of plaque in the aortic root, aortic arch, and thoracic aorta. Interestingly, mice with a normal diet fared better with CSNP therapy at the aortic root and aortic arch while high-fat diet mice only reflected an improvement at the aortic root.

As CSNP nanotechnology has shown promising outcomes in mice models, it would be interesting to see how its application in human subjects will proceed. Significant to note for this nanotech pharmaceutical's compatibility and use in mice was addressing the most opportune chemical structure and bonding of statin and cyclodextrin in addition to using a dose-effective but least adverse quantity of cyclodextrin. These biochemical aspects along with evaluating the best combination of encapsulated medication and lifestyle modification can help propel CSNP to be integral in CVD treatment and management.

Apart from Cargo-switching nanoparticles, the therapeutic focus has shifted from novel innovations to existing anti-inflammatory agents. CANTOS trial challenged the theory of targeting atherosclerosis through reducing inflammation by conducting a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β [59]. It recruited 10,061 patients with a history of myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter [59]. The trial tested the endpoint efficacy of non-fatal cardiovascular and neurological outcomes after 3 different doses of canakinumab compared to a placebo group [59]. After 48 months of trial, reduction of baseline in high-sensitivity C-reactive protein was seen in all three groups receiving varying doses of the drug [59]. A 26% reduction was reported in the group that received the 50-mg dose of canakinumab, 37% in the 150-mg group, and 41% in the 300-mg group compared to the placebo group. However, Canakinumab did not reduce lipid levels from baseline [59]. At a median follow-up of 3.7 years, the incidence rate for the primary endpoint was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group [59]. Yet, statistically significant results for the primary endpoint were only achieved in the 150mg group [59]. In addition, Canakinumab was associated with a higher incidence of fatal infection than placebo, questioning its efficacy in targeting atherosclerosis in CAD.

## Discussion

Targeted nanotherapy against inflammation-induced atherosclerosis has been at the forefront of cardiovascular therapeutic innovation. Unlike traditional lipid-lowering agents, the use of nanotechnology reduces lesional inflammation in addition to scavenge lipids within atherosclerotic plaque. Although in vivo studies have shown substantial benefits in mice models, some of these studies have yet to reach human subjects or shown little efficacy in the early phase of clinical trials. Much of the discrepancy in efficacy can be attributed to the multiple biological barriers of using nanotechnology. While in circulation, physiological properties such as blood flow, excretion, and the presence of phagocytic cells can greatly reduce the bioavailability of nanoparticles. To avoid clearance from the immune system, some nanoparticles have been PEGylated, however, humans can have performed antibodies or build anti-PEG antibodies de novo, making these nanoparticles prone to rapid excretion by the immune system [60]. Even within the vasculature, the shear stress from the rapid blood flow can damage the cargo and strip nanoparticles from their surface coating preventing them to localize within the targeted sites. Once localized, nanoparticle uptake and internalization may vary widely due to the microenvironment of the lesion. This is due to the dynamic nature of the cytoskeleton of the cells that respond to external cues within the microenvironment [60]. Thus, nanoparticles interacting with the same cell may experience different interactions depending on their location on the cell's membrane or their time of contact; determining the nanoparticle's therapeutic potential. Furthermore, once interaction has been established, the internalization of the nanoparticle varies depending on the size of the particle. Smaller size proves to have better internalization but their cytotoxic effects are larger [60]. While these barriers may be overcome through precision engineering, barriers involving commercialization costs in developing and marketing a nano-drug may require much more involvement in the practicality of this innovation [61]. Perhaps, much of the reason why very few nano-technology studies have reached clinical trials despite the numerous proposals existing in literature to date.

Advancements in pharmacotherapy were limited to the use of existing anti-inflammatory agents in the management of atherosclerosis. Multiple studies provide evidence that the use of systemic anti-inflammatory agents has the potential to reduce lipid-rich necrotic core [36,62,63]. However, by their very nature, anti-inflammatory drugs may predispose patients to opportunistic infections and delay wound healing. This is in addition to off-target adverse effects such as removal of RBCs with anti-CD47 antibodies, making it difficult to create a benefit-risk balance [36,40]. While current management with statins delays the progression of atherosclerotic disease, it is clear that vascular-specific agents should be the focus of next-generation therapeutics in targeting direct inflammation.

Currently, many of these innovative designs are still being researched and not in human clinical trials. Notably, a lot of these therapeutics and interventions were difficult to find and not gleaned from recent articles. More recently published work has been laboratory research or reviews previously published studies. Some of the data available are of research groups evaluating the effectiveness of a grant-funded idea. These studies were performed on mice or pig models with reference to only potential therapeutic benefits in humans. It would be interesting to have more papers providing data on the course of previous intervention, at what stage difficulties in evaluation occurred and why, and whether their therapeutic idea led to another innovation. Such as, the success of newer innovations involving nanotechnology was only limited to pre-clinical data, without any reference to clinical trials. Anti-inflammatory agents currently in use for autoimmune diseases and carcinomas have shown cardioprotective effects yet the extent of these benefits has not been explored in much detail. Thus, emergent therapies and therapies with potential benefits in the management of atherosclerosis must be explored in large cohorts in prospective studies.

## Conclusion

Cardiovascular Disease is a pervasive and prominent disease within society that often skips primordial prevention and is addressed at the primary and secondary levels of prevention. Management then is defined by assessing the individual's risk factors which can be compounded or exacerbated by other comorbidities. Therefore, it is integral that better routine screenings

and application of patient algorithms should be utilized to provide timely intervention.

These patient profile complexities impact the available care and could lead to limitations to therapy. At times, these therapies are contraindicated due to intrinsic factors that can negatively affect the patient's baseline health or simply may not be applicable. For example, standard therapeutics after stent placement includes aspirin and clopidogrel or ticagrelor which can adversely affect wound healing or cause ulceration. Moreover, as these health issues are often found when there are compounding factors, additional medications for blood pressure management might be added. The increasing medication load, especially in the elderly, can facilitate systemic and central nervous system issues. In addition, some patients are poor candidates to receive a Coronary Artery Bypass Graft (CABG). At times, this ineligibility could be due to the patient being unable to tolerate dual antiplatelet therapy.

There have been improvements to the stent material and pharmaceuticals available to treat CVD but improvements can still be made. Thus, emerging therapeutic interventions such as stent dynamics, nanotechnology, and nanopharmacology are being evaluated. While these new innovations are exemplary and exciting, they need to be optimally beneficial for manufacturing and production. Patients can struggle with costs related to their health management which means a treatment plan needs to be advantageous and affordable. It would be advantageous to follow the highlighted nanomaterials, nanopharmaceuticals, Cargo-Switching Nanoparticles to see which progress to human trials, are reproducible, and are cost-effective.

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