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REVIEW

Lipid-based nanosystems for atherosclerosis treatment: Evolving approaches and novel therapeutic strategies

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Clinical application

Abstract Atherosclerosis, the leading cause of cardiovascular diseases, has become increasingly prevalent worldwide, driving the need for innovative therapeutic strategies to improve clinical outcomes. Lipid-based nanosystems have emerged as promising drug delivery platforms due to their biocompatibility, versatility, and proven clinical track records. Among them, traditional systems such as liposomes have been extensively applied in atherosclerosis therapy, primarily for their well-established safety profile and their capacity to deliver both hydrophilic and hydrophobic agents. However, emerging research has expanded the scope of lipid-based nanosystems to include lipid nanoparticles, lipoprotein-based nanosystems, cell membrane-coated nanosystems, and so on. These systems have demonstrated great promise in addressing the complex and heterogeneous nature of the disease. This review aims to provide a comprehensive overview of lipid-based nanosystems, from traditional formulations to cutting-edge innovations, and their evolving applications in the treatment of atherosclerosis. We also discuss the challenges

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associated with the clinical translation of these systems, as well as future prospects for developing more effective and personalized therapeutic strategies. In conclusion, lipid-based nanosystems provide a promising option for atherosclerosis treatment, potentially driving the progress of novel therapeutic strategies.

1. Introduction

Cardiovascular disease has emerged as the leading cause of death worldwide, with atherosclerosis (AS) being the primary pathological basis of cardiovascular mortality[1]. Atherosclerotic lesions are initiated by endothelial injury and subendothelial lipoprotein retention (Fig. 1)[2]. Subsequently, monocytes are recruited by chemokines into the subendothelial space and differentiated into macrophages, which internalize oxidized low-density lipoprotein (ox-LDL) to form foam cells[3]. Immune cells also secrete pro-inflammatory cytokines and signal molecules to induce a series of immune responses, further complicating the pathophysiology[4]. Finally, the vulnerable plaque necrotic core surrounded by a fibrous cap is exposed to the bloodstream and platelets and may cause thrombosis[5]. Collectively, the development and progression of AS are affected by various factors such as abnormal lipid metabolism, inflammatory response, endothelial dysfunction, vascular smooth muscle cell proliferation, and oxidative stress, thereby limiting the effectiveness of therapeutic interventions. Current anti-AS drug treatments, including lipid-lowering drug therapies (*e.g.*, statins and PCSK9 inhibitors), platelet aggregation inhibitors (*e.g.*, acetylsalicylic acid), antihypertensive drugs (*e.g.*, angiotensin-converting enzyme inhibitors), and antidiabetic drugs (*e.g.*, thiazolidinediones), have been extensively investigated and implemented in clinical practice[6]. However, the off-target effects of these therapies frequently cause side effects, such as liver damage, arrhythmia, gastrointestinal bleeding, and muscle discomfort. Furthermore, single-target therapies are often insufficient for addressing the multifaceted pathological environment characteristic of AS. More precise and effective therapeutic strategies are essential for addressing the pathological mechanisms underlying AS, including lipid metabolism disorders, chronic inflammation, and immune dysregulation. Therefore, there is an urgent need to develop efficient therapeutic methods to reduce adverse reactions and improve the treatment performance of AS.

Nanotechnology-based drug delivery systems have attracted significant research interest as innovative strategies for cardiovascular care due to their advancements in pharmaceutical stability, accurate delivery mechanisms, and minimized off-target interactions[7]. Polymeric nanoparticles, known for their stable drug release profiles and prolonged therapeutic effects, have been widely utilized for anti-AS drug delivery[8,9]. Magnetic nanoparticles used as contrast agents can enhance magnetic resonance imaging (MRI) capabilities and may further improve therapeutic outcomes when combined with other nano-delivery systems[10]. Notably, lipid-based nanosystems have been among the most successful nanomedicines developed, demonstrating significant clinical achievement in treating cancer, viral infections, and genetic diseases[11]. Liposomes were the first nanomedicine formulation approved by the FDA, ushering in a new era of targeted nanotherapeutics, particularly in oncology. Over subsequent decades, advancements in theoretical understanding and technological innovations have led to the development of diverse lipid-based nanosystems, including solid lipid nanoparticles (SLNs), micelles, nanoemulsions, lipid nanoparticles (LNPs), and so on. Lipid-based nanosystems are generally defined as nano-sized structures primarily composed of lipid molecules. They offer three major advantages: 1) High biocompatibility and low immunogenicity, as

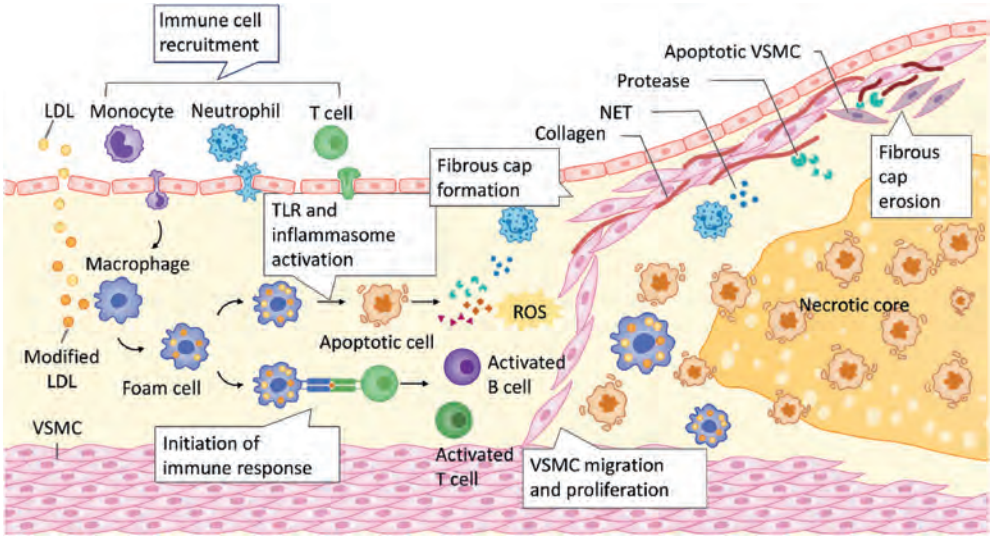

Figure 1 The progression of atherosclerotic lesions. VSMC, vascular smooth muscle cell; NET, neutrophil extracellular trap; LDL, low-density lipoprotein; TLR, toll-like receptor; ROS, reactive oxygen species.

their lipid composition resembling natural biological membranes, facilitating safe systemic administration; 2) Versatile drug encapsulation, enabling efficient loading of both hydrophilic and hydrophobic agents through structural modulation; and 3) High functional adaptability, allowing surface engineering for targeted delivery, responsiveness to pathological stimuli (*e.g.*, ROS, pH).

In the context of AS, the lipid nature of these systems endows them with inherent biocompatibility and the capability of interacting with the lipid-rich environment of atherosclerotic plaques, allowing for more efficient drug accumulation in the deep lipid-rich necrotic cores of plaques[12]. The recent advances in LNPs have demonstrated significant promise in targeted delivery to inflammatory and immune cells within plaques[13]. Additionally, the intrinsic biochemical activities of lipid nanomaterials make them particularly suited for multiple strategies combination aimed at simultaneously addressing multiple pathological mechanisms underlying AS. Given these unique characteristics, lipid-based delivery systems are uniquely positioned to overcome existing therapeutic limitations and significantly advance AS treatment strategies. This review aims to summarize recent advances in lipid-based nanosystems for AS, focusing on their design and application (Fig. 2). We will discuss the evolution of lipid formulations from traditional preparations to cutting-edge nanosystems, highlighting their potential to address the complex pathophysiology of AS. Additionally, the challenges and prospects of clinical translation for lipid-based nanocarriers in treating AS will be explored, emphasizing the need for further innovation in drug delivery technologies.

2. Traditional lipid-based nanosystems

Traditional lipid-based nanosystems represent the foundational generation of these delivery systems, as shown in Table 1[14-24], and are typically composed of common lipids such as phospholipids, cholesterol, and other naturally existed or simply synthesized lipid compounds. These nanocarriers primarily rely on lipid nanostructure to enhance drug solubility and improve pharmacokinetic profiles, thus gaining a foothold in improving the therapeutic efficacy of conventional anti-atherosclerosis drugs.

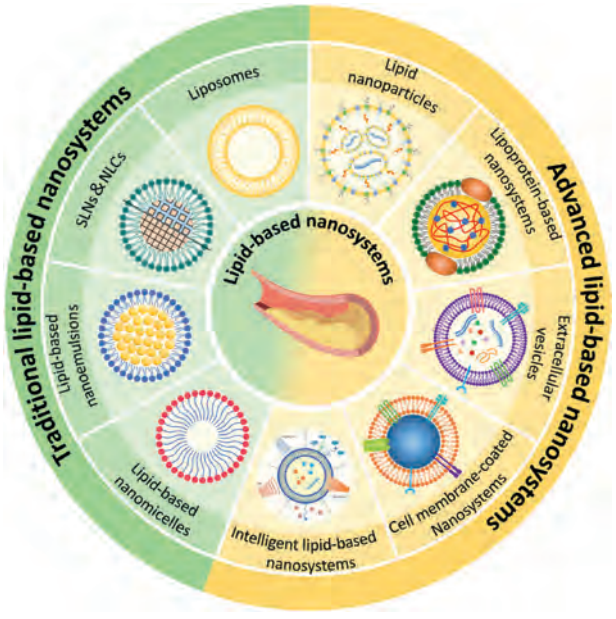

Figure 2 A schematic overview of lipid-based nanosystems used to treat AS. SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers.

2.1. *Liposomes*

Liposomes are hollow vesicles formed by the self-assembly of phospholipid bilayers, whose hydrophobic tails and hydrophilic heads enable simultaneous loading of lipophilic and hydrophilic drugs, addressing challenges in drug solubility and stability[25]. The hydrophobic bilayer encapsulates lipophilic drugs, while the aqueous core efficiently entraps hydrophilic agents through phase separation techniques[26]. Surface modification with polyethylene glycol creates long-circulating liposomes to prolong systemic circulation and evade immune clearance[27], whereas conjugation with antibodies or ligands achieves active targeting.

2.1.1. *Passive targeting*

The increased vascular permeability at the site of atherosclerotic plaques, coupled with impaired lymphatic drainage, facilitates the accumulation of liposomes at the plaque site and allows them to remain there for an extended period[28]. This, in turn, enhances the concentration of the drug at the site of the lesion. Docosahexaenoic acid (DHA) is an omega-3 polyunsaturated fatty acid. It is recommended by the American Heart Association as a dietary supplement for AS treatment based on its anti-inflammatory and antioxidant properties. However, its poor stability and poor intestinal absorption limit its therapeutic effect. As liposomes preferentially target cells of the mononuclear phagocytic system, such as macrophages, Wang et al.[29] developed an injectable DHA liposome nanomedicine which significantly alleviated atherosclerotic plaques in mice, enhancing the therapeutic efficacy and bioavailability of DHA. Another research group designed ROS-eliminating liposomes (Tempol-Lips) to attenuate inflammation *via* scavenging overproduced intracellular ROS (Fig. 3A)[30]. Tempol-Lips exhibited preferential biodistribution in atherosclerotic plaques of *Apoe*$^{-/-}$ mice *via* a passive targeting mechanism (Fig. 3B)[30], demonstrating greater attenuation of atherosclerotic disease progression compared with the control group. Although passive targeting seems useful, the accumulation of nanoparticles may be limited by the endothelial remodeling as the disease progresses[31]. Therefore, more researchers focus on the active targeting strategies.

2.1.2. *Active targeting*

Active targeting strategies leverage the overexpression of specific receptors or molecules in atherosclerotic plaques to achieve precise drug delivery. For instance, CD44, a receptor highly expressed on vascular endothelial cells, smooth muscle cells, and macrophages in plaques, can be targeted using hyaluronic acid (HA)-modified liposomes[32]. YN001, a CD44-targeted liposome encapsulating rosuvastatin calcium, has shown remarkable efficacy in preclinical studies. It binds to CD44 with a high affinity (K_D = 485.5 pmol/L), enabling targeted enrichment of rosuvastatin in plaques[33]. In *Apoe*$^{-/-}$ atherosclerotic mouse models, YN001 demonstrated higher drug concentrations in aortic plaques compared to non-targeted liposomes, leading to enhanced cholesterol efflux and reduced inflammatory markers like monocyte chemoattractant protein-1[33]. This targeted approach not only improves therapeutic efficacy but also minimizes systemic side effects. An additional innovative strategy involves the use of

Table 1 The characteristics of traditional lipid-based nanosystems.

Type	Main component	Structure	Advantage	Limitation	Ref.
Liposomes	Phospholipids; cholesterol	Lipid bilayer vesicle with aqueous core	Versatile drug encapsulation; Modifiable surface; Biocompatible	Drug leakage; rapid clearance by reticuloendothelial systems without PEGylation	14−16
SLNs	High-melting solid lipids; surfactants	Solid lipid core stabilized by surfactants	Good stability; Controlled release; Scalable	Low drug load; drug release caused by polymorphic transitions	17,18
NLCs	Solid and liquid lipids; surfactants	Hybrid matrix of solid and liquid lipids	High drug load; Improved retention over SLNs; Reduced expulsion; Suitable for chronic use	More complex formulation than SLNs; Restricted excipient choices	19,20
Lipid-based nanoemulsions (LNEs)	Phospholipids; cholesterol; Surfactants	Oil-in-water nanoemulsion droplets	Enhanced bioavailability; Suitable for multiple administration	Limited targeting ability; Low physical stability; Poor hydrophobic drug loading	21,22
Lipid-based nanomicelles (LNMs)	Amphiphilic lipids; surfactants	Monolayer micelle-like aggregates	Simple preparation method; Responsive delivery	Low stability; Poor loading; sensitive to physiological environment	23,24

SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers; LNEs, lipid-based nanoemulsions; LNMs, lipid-based nanomicelles.

cRGD-modified liposomes. The cRGD peptide specifically interacts with integrin $\alpha v\beta 3$, a receptor that is highly expressed on endothelial cells and macrophages within atherosclerotic plaques. Shi et al.[34] designed cRGD-modified liposomes encapsulating Sivelestat, a neutrophil elastase inhibitor, to target neutrophils and inflammatory cells within plaques. These liposomes actively hitchhiked neutrophils to deliver Sivelestat to plaque sites, significantly reducing inflammation and plaque progression. Similarly, vascular cell adhesion molecule-1 (VCAM-1)-targeted liposomes, functionalized with VHPKQHR peptides, have been developed to target inflamed endothelial cells[35,36]. Chen and colleagues[35] employed the targeting peptide VHPKQHR to alter phospholipid molecules for VCAM-1 targeting and incorporated ultrasmall paramagnetic iron oxide (USPIO/Fe_3O_4) along with rapamycin into a formulation known as Rap/Fe_3O_4@VHP-Lipo (Fig. 3C). Benefiting from targeting peptide, Rap/Fe_3O_4@VHP-Lipo aggregated at the plaques and released the most Rap, leading to the markedly diminished aortic fluorescence intensity and the reduced blood lipid levels (Fig. 3D and E)[35]. P-selectin is another highly expressed receptor in endothelial cells in atherosclerotic plaques. By modifying the surface of liposomes with ligands that can bind to P-selectin, targeted delivery to plaques can be achieved[37]. Low molecular weight fucoidan is a marine polysaccharide that can specifically bind to P-selectin. Liu et al.[38] introduced a low molecular weight fucoidan coupled PEGylated liposomes (LMWF-Lip) encapsulating berberine hydrochloride. After being administered *via* tail vein injection, LMWF-Lip can be effectively internalized by the activated vascular endothelial cells and inhibit the expression of P-selectin, indicating a therapeutic potential to treat inflammatory diseases such as AS.

2.2. *SLNs and nanostructured lipid carriers (NLCs)*

SLNs and NLCs are two lipid-based nano-delivery systems distinguished by their composition and microstructure[39]. SLNs consist of high-melting-point solid lipids, including triglycerides, fatty acids, and waxes, to form a highly ordered crystalline matrix at ambient/body temperature, with drugs typically distributed as solid solutions or drug-enriched cores[40]. However, their rigid structure limits drug-loading capacity and may trigger drug expulsion during storage due to polymorphic transitions. In contrast, NLCs, as second-generation SLNs, incorporate liquid lipids, like oleic acid or isopropyl myristate, to replace partial solid lipids, resulting in imperfect crystalline, amorphous, or multiple-type hybrid matrices[41]. These structural defects significantly enhance drug-loading efficiency while minimizing leakage and preserving sustained-release properties.

Up to now, researchers have proved that SLNs and NLCs can improve the biodistribution of cardiovascular drugs in *Apoe*$^{-/-}$ mice and are utilized for both drug and contrast agent carriers[42-44]. Oumzil et al.[44] explored a novel approach using nucleoside-lipids to synthesize SLNs loaded with iron oxide and therapeutic agents for MRI-guided treatments. The incorporation of nucleoside-lipids enabled the formation of stable SLNs carrying prostacycline, which inhibits platelet aggregation. These SLNs exhibited superior relaxivity compared to the clinical contrast agent Feridex (2.6-fold higher transverse relaxivity), highlighting their potential for image-guided therapy. Similarly, ^{64}Cu-labelled NLCs were developed to test the efficiency as a drug and contrast agent carrier (^{64}Cu-B22280-NLCs) in the atherosclerotic murine model[43]. The authors found that ^{64}Cu-B22280-NLCs were highly co-localized with lipid staining, representing an attractive approach for targeting atherosclerotic lesions[43].

Notably, some reports find that SLNs and NLCs may have specific therapeutic advantages as synthetic mimics of lipoproteins for AS treatment. du Toit et al.[45] synthesized a fenofibrate-loaded solid lipid nanoparticle coated with anti-ox-LDL antibodies. The nanoparticles were delivered *via* an osmotic pump device implanted in the jugular vein of Large White pigs, serving as an Intra-Vascular Implantable Sensor and Drug Delivery Device (IVISDDD) to regulate systemic low-density lipoprotein (LDL) cholesterol[45]. The IVISDDD released fenofibrate in response to

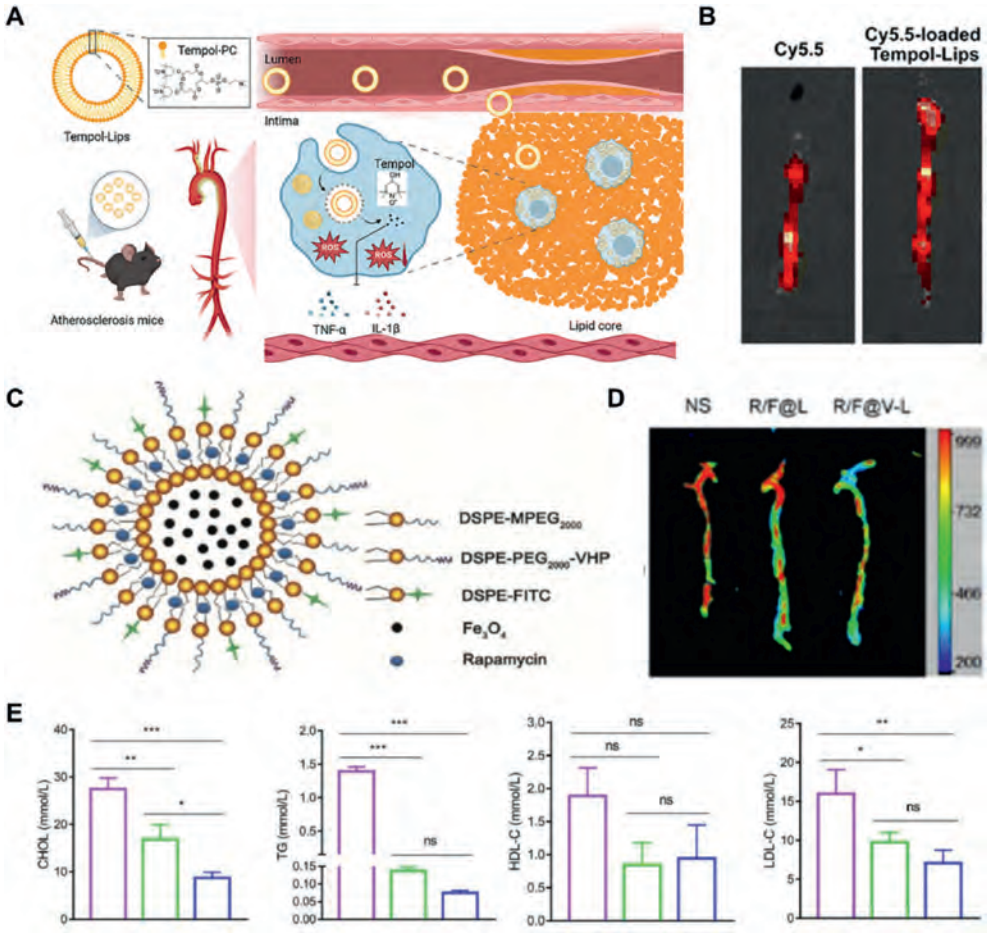

Figure 3 Passive and active targeting liposomes for AS treatment. (A) Schematic illustration of Tempol-Lips intervening redox-modulation for AS treatment. (B) *Ex vivo* fluorescence images show that Tempol-lips perform a better accumulation. (A, B) are reproduced with permission from Ref. 30. Copyright © 2023 under the Creative Commons license. (C) Structure diagram of Rap/Fe_3O_4@VHP-Lipo. (D) The aortic fluorescence intensity observed in the Rap/Fe_3O_4@VHP-Lipo group was markedly diminished. (E) The level of total cholesterol (CHOL), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) in the plasma. (C—E) are reprinted with permission from Ref. 35. Copyright © 2022 under the Creative Commons license.

the uptake and degradation of anti-LDL SLNs—LDL complexes, leading to a significant 29.9% decrease in total cholesterol, attributed to a 37.4% drop in LDL and a concurrent rise in high-density lipoprotein (HDL) levels[45]. Based on the previous research, Zhang and colleagues[46] developed an HDL resembling NLCs as an alternative to SLNs to improve the delivery of Tanshinone IIA (TA). They confirmed TA-NLCs could bind to apolipoprotein A-I (ApoA-I) specifically, escaping from recognition by macrophages[46]. Furthermore, they published another paper to prove that NLCs could deliver lovastatin, a hydrophobic anti-atherogenic drug, to foam cells[12]. These results indicated that HDL-mimicking NLCs would be a desirable delivery vehicle for lipophilic cardiovascular drugs. The potential of SLNs and NLCs to target atherosclerotic lesions has not been systematically investigated.

2.3. *Lipid-based nanoemulsion (LNEs)*

LNEs leverage the amphiphilic nature and biocompatibility of lipid components to achieve multifunctional applications in AS therapy. The lipid matrix not only serves as a drug carrier but also enhances bioavailability and enables targeted delivery through its inherent physicochemical properties[21]. Combining these features to design LNEs in the treatment of AS has also been validated in many experiments. Leite et al.[47] demonstrated that the combined treatment of LNEs-encapsulated methotrexate and LNEs-encapsulated etoposide achieved a 95% reduction of aortic lesion areas compared with controls. In another study, LNEs-paclitaxel attenuated atherosclerotic lesion burden by 60%, reduced the intima-media ratio by fourfold, and inhibited macrophage migration as well as smooth muscle cell proliferation and invasion into the intima[48]. 1,8-Cineole has antioxidant, anti-inflammatory, and cholesterol-modulating effects, with ameliorative effects on vascular injury, and has the potential for preventing the progression of AS; however, its low oral bioavailability and short half-life limit its clinical application due to its high volatility and instability[49]. To solve this problem, Chen et al.[50] designed a nanoemulsion injection to improve the stability, the residence time in the gastrointestinal tract and the permeability of 1,8-cineole. These LNEs loaded 1,8-cineole successfully demonstrated significant therapeutic efficacy in the AS mouse model.

Besides the conventional enhancement of drug bioavailability, LNEs can also be used as a tool to strengthen AS detection. At present, due to technological limitations, atherosclerotic plaques are only diagnosed when serious complications (*e.g.*, stroke or myocardial infarction) occur[51]. Therefore, Bonnet et al.[52] designed a nanoemulsion carrying a fully human scFv-Fc antibody to achieve targeted enrichment of atherosclerotic plaques. The incorporation of nanoemulsions successfully achieved strong MRI signals both *in vitro* and *in vivo*. The LNEs formulated in this study offer novel strategies for non-invasive targeted imaging and synergistic therapeutic applications in AS. Furthermore, Prévot et al.[53] designed a nanoemulsion loaded with magnetic nanoparticles and modified with human scFv-Fc TEG4-2C antibodies for magnetic particle imaging and MRI. LNEs selectively bind atheroma plaque both *in vitro* and *ex vivo* in animal models of AS, confirming their potential as a new contrast agent.

2.4. Lipid-based nanomicelles (LNMs)

Supramolecular assemblies formed through the spontaneous organization of amphiphilic lipid derivatives constitute LNMs. They have garnered substantial attention in AS therapy owing to their excellent biocompatibility, ease of preparation, and capacity for stimuli-responsive drug release. Phospholipase is a significant biomarker in AS progression[23]. Lechuga-Vieco et al.[23] designed a phosphatidylcholine-coated nanomicelles (IOPC-NM) used for the specific characterization of AS plaque. The results show that the phospholipid coating nanomicelles were selectively aggregated and accumulated in the atheroma lesion with high phospholipase expression. It indicates the possible use of IOPC-NM as a probe for characterizing cellular traffic in the atherosclerotic plaque. In another study, Muñoz-Hernando et al.[54] developed a sphingomyelin-based nanomicelle capable of being activated by sphingomyelinase within atherosclerotic plaques. The accumulation of these LNMs in the plaque *via* sphingomyelinase enzymatic action was confirmed by fluorescence, MRI imaging, and electron microscopy. These findings underscore the targeting potential of LNMs for atherosclerotic lesions attributed to the presence of phospholipase and sphingomyelinase. Despite promising results, the number of published studies concerning the administration potential of LNMs in AS is still limited. Some studies tend to apply polymeric nanomicelles for efficient therapy. However, the potential hazard of polymeric nanomicelles for the cardiovascular system causes concern[55]. Therefore, hybrid nanomicelles are a more common form. Fu and associates[56] utilized amphiphilic polymers (Distearoyl peptide modified PEG2000-amide, DSPP) that self-assemble into nano-scale for the delivery of ROS-responsive prodrugs (Citop-NMs). The superhydrophobic lipid domain of the amphiphilic polymers facilitated hydrophobic drug loading, while the hydrophilic shell improved systemic circulation stability. Citop-NMs show prolonged blood circulation duration and enhanced targeted delivery to AS plaques, resulting in superior therapeutic efficacy compared to conventional treatments.

3. Advanced lipid-based nanosystems

In the previous section, we have introduced traditional lipid nanosystems that are applied in AS. Traditional types indicated carriers are composed of lipids with the capability to deliver certain drugs and improve the therapeutic effect compared with free drugs. Nevertheless, traditional carriers have limited application because of their weak active targeting ability and difficulty in delivering biomolecules. In contrast, advanced delivery systems achieved enhanced therapeutic results by integrating biologically active components and efficiently delivering large molecules (nucleic acids and proteins), which have a better prospect for the AS administration (Table 2)[57-70]. These advanced lipid-based nanosystems, integrating biomimetic, environment-responsive, and gene modulation strategies, represent the future direction of precision, real-time, and personalized therapy for AS.

3.1. LNPs

LNPs are a type of lipid-based delivery system that differs from traditional liposome[15]. Their solid lipid matrix structure is composed of ionizable lipids, phospholipids, cholesterol, and PEG-lipids. LNPs are prepared *via* rapid microfluidic mixing of lipid−ethanol and aqueous nucleic acid solutions (typically at a 3:1 flow ratio), resulting in uniform particle sizes[71]. The ionizable lipids (accounting for 30%−70% of the total lipids) play a core role through a pH-dependent charge-reversal mechanism[72]: under acidic formulation conditions, the protonation of tertiary amine groups imparts a positive surface charge, enabling efficient electrostatic complexation with negatively charged nucleic acids. At physiological pH, these lipids adopt a near-neutral charge state, thereby exhibiting low cytotoxicity. Following cellular uptake through endocytosis, exposure to the mildly acidic endosomal environment (pH 5.0−6.5) leads to re-protonation, triggering lipid phase transitions and promoting endosomal membrane destabilization and cytosolic release of the nucleic acid cargo (Fig. 4A). LNPs have attracted great attention in the treatment of AS due to their potential to achieve precise and personalized therapeutic effect.

The liver and immune organs, as reticuloendothelial systems, are the main natural accumulation sites for LNPs, making them especially suitable for systemic modulation of lipid metabolism and the immune pathway to treat AS[73]. For instance, Musunuru et al.[74] encapsulated CRISPR adenine base editor in LP01 lipid-based LNPs to treat living cynomolgus monkeys, observing an obvious knockdown of PCSK9 in the liver and reduced LDL cholesterol level in the plasma. Similarly, lipidoid $98N_{12}$. LNPs-encapsulated *PCSK9* siRNA demonstrated durable silencing effects (50%−70% mRNA reduction persisting for 3 weeks post-dose) in rodent models, significantly lowering plasma cholesterol levels (Fig. 4B and C)[75]. Another research group delivered C−C motif chemokine receptor 2 (CCR2) siRNA using C12-200-based LNPs to inflammatory monocytes in the spleen and marrow, resulting in targeted *CCR2* knockdown, reduced macrophage accumulation at atherosclerotic plaques, and a 38% decrease in lesion size in the aortic root[76]. These studies validate LNPs as potent tools for indirect AS intervention *via* systemic modulation. However, this liver-dominant biodistribution also limits direct targeting of atherosclerotic plaques, necessitating engineering strategies to redirect LNPs to vascular lesions.

To overcome the inherent hepatic accumulation of LNPs, recent designs have introduced diverse targeting strategies to redirect their delivery toward atherosclerotic plaques. Zhang's group[77] functionalized *IL*-10 mRNA-loaded LNPs with mannose ligands, enabling specific uptake by plaque-resident macrophages. The *in vitro* results indicated that *IL*-10 mRNA with active targeting activity performed significantly higher transfection efficiency than unmodified LNPs preparation (Fig. 4D−F)[77]. To precisely target lesional macrophages, Tao et al.[78] conjugated an

Table 2 The characteristics of advanced lipid-based nanosystems.

Type	Main component	Structure	Advantage	Limitation	Ref.
LNPs	Ionizable lipids; phospholipids; cholesterol; PEG-lipid	Lipid vesicle with solid core	Efficient nucleic acid delivery; endosomal escape facilitated by pH-responsive ionizable lipids	Poor loading of small hydrophilic drugs; Liver-dominant biodistribution	57,58
HDL-based delivery systems	Phospholipids; cholesterol; apolipoproteins or peptide mimics	HDL-like nanoparticles	Mimic endogenous HDL; enable cholesterol efflux; high biocompatibility; Passive targeting	Sophisticated production process; Bad reproducibility; Stability issues under physiological conditions	59−61
LDL-based delivery systems	Phospholipids; cholesterol; ApoB or LDL-mimicking components	LDL-like nanoparticles	Target LDL receptors; Allow delivery of lipophilic (*e.g.*, statins, paclitaxel) to plaques	Possible immune recognition; Limited drug-loading diversity	62−64
EVs	Exosomes; microsomes or apoptotic bodies of natural origin	Lipid vesicles	Inherent targeting; improved plaque selectivity; Minimal immunogenicity	Heterogeneity and scalability issues; Source-dependent composition	65−67
Cell membrane-coated nanosystems	Phospholipids; cholesterol; Source-specific cell membranes	Core−shell nanoparticles	Homotypic targeting *via* membrane proteins; Prolonged circulation; immune evasion	Challenging extraction and purification	68,69
Intelligent lipid-based nanosystems	Responsive lipid materials (*e.g.* ROS/pH-sensitive lipids)	Varies (vesicular or hybrid forms)	Controlled release triggered by stimuli (*e.g.*, ROS, enzymes, pH) to enhance site-specific therapy	Complexity of synthesis	70

LNPs, lipid nanoparticles; HDL, high density lipoprotein; LDL, low density lipoprotein; ApoB, apolipoprotein B; EVs, extracellular vesicles; ROS, reactive oxygen species.

S2P peptide, which recognizes the macrophage receptor stabilin-2, to the lipid-PEG layer to generate LNPs for *CaMKII*γ siRNA delivery. These S2P-modified LNPs exhibited a two-fold increase in macrophage uptake and restored MerTK expression, thereby rescuing macrophage phagocytosis, enhancing fibrous cap integrity, and reducing lesion area *in vivo*. Furthermore, Dahlman et al.[79] constructed a high-throughput library of epoxide-modified lipid−polymer hybrids, identifying 7C1 as a lead candidate for endothelial cell transfection. 7C1-based nanoparticles (Fig. 4G)[79] effectively silenced target genes in endothelial cells both *in vitro* and *in vivo*, demonstrating pronounced colocalization with inflamed endothelial cells. Building on this, Chen and colleagues[80] employed 7C1 nanoparticles to deliver *TGF-*β siRNA in *Apoe*$^{-/-}$ mice, resulting in reduced plaque burden and lipid deposition (Fig. 4H). Collectively, these studies illustrate how ligand-mediated targeting, lipid composition engineering, and surface functionalization can be strategically integrated into LNP design to achieve precise and cell-specific delivery in AS therapy.

3.2. *Lipoprotein-based nanosystems*

Lipoproteins, including HDL, LDL, very low-density lipoprotein, and intermediate-density lipoprotein, are natural nanoparticles composed of a lipid core and an outer layer of phospholipids and cholesterol. Their unique biomimetic properties, including biocompatibility, biodegradability, non-immunogenicity, and inherent targeting capabilities, make them highly attractive for drug delivery applications[81]. Among them, HDL and LDL have demonstrated the most significant potential as drug carriers, particularly in AS treatment. However, isolating native HDL and LDL from plasma is complex, expensive, and poses risks of contamination. To address this, researchers have developed synthetic and reconstituted lipoproteins (rHDL and rLDL) by using apolipoproteins, phospholipids, and cholesterol in combination with self-assembly or microfluidic technologies, enabling precise control over particle size, distribution, and lamellarity[82,83].

3.2.1. *HDL-based delivery systems*

HDL, the smallest and densest lipoprotein (7−13 nm), is recognized as "good cholesterol" due to its critical role in reverse cholesterol transport, as well as its anti-inflammatory and antioxidant properties[61,84,85]. Leveraging these natural functions, HDL-based drug delivery systems have been designed to improve AS treatment outcomes. One of the major breakthroughs in this area was achieved by Duivenvoorden, who designed the first rHDL-based statin delivery system for targeted anti-inflammatory effects in atherosclerotic plaques (Fig. 5A and B)[86]. Their studies demonstrated that rHDL-mediated statin delivery significantly reduced inflammation in late-stage AS, decreasing plaque area by 31% compared to placebo groups (Fig. 5C and D)[86]. To further optimize cholesterol metabolism and drug release, β-cyclodextrin (β-CD) has been incorporated into rHDL[87,88]. He et al.[88] designed an rHDL-based β-CD-loaded system that enhanced cholesterol efflux from foam cells while delivering simvastatin, effectively restoring cellular cholesterol homeostasis.

In addition to synthetic and reconstituted HDL, peptide-based HDL mimetics have emerged as a promising alternative. These peptides are designed to mimic the structure and function of

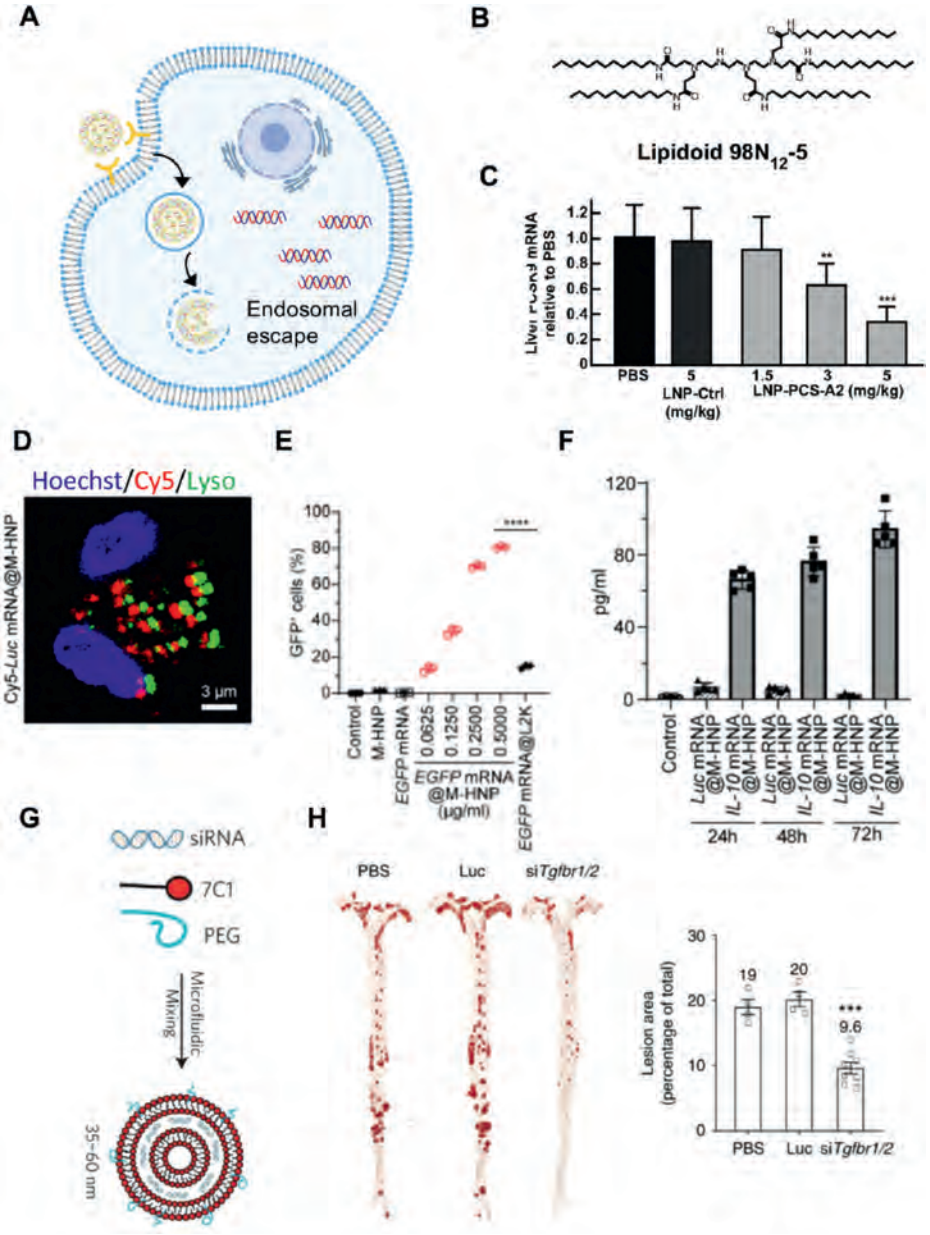

Figure 4 LNPs for AS treatment. (A) Schematic diagram of endosomal escape mechanism of LNPs. (B) The structure of lipidoid 98N12-5. (C) Dose-dependent decrease in hepatic *PCSK9* mRNA (relative to controls) 2 days after dose. (B, C) are reproduced with permission from Ref. 75. Copyright © 2008, National Academy of Sciences. (D) The images of bone marrow-derived macrophages at 4 h after incubation with NPs incorporated with Cy5-labeled *Luc* mRNA (red). (E) The percentage of GFP-positive cells in BMDMs was assessed using FlowJo software. (F) ELISA analysis for IL-10 levels in BMDMs treated with *Luc* mRNA@M-HNPs or *IL*-10 mRNA@M-HNPs for 24, 48, or 72 h. (D–F) are reprinted with permission from Ref. 77. Copyright © 2023, American Chemical Society. (G) Schematic diagram of "7C1" nanoparticles design and self-assembly. Reprinted with permission from Ref. 79. Copyright © 2014, Springer Nature Limited. (H) Representative images of the ORO-stained atherosclerotic plaques in the aorta (left) along with their corresponding quantification (right). Reprinted with permission from Ref. 80. Copyright © 2019, The Author(s), under exclusive license to Springer Nature Limited.

ApoA-I, the primary protein component of HDL. One of the most studied HDL-mimetic peptides is ApoA-I mimetic peptide 4F (4F), a short peptide that mimics the lipid-binding and anti-inflammatory properties of ApoA-I[89]. When the 4F peptide forms discoidal complexes with phospholipids, it not only protects ApoA-I from oxidative damage but also improves HDL function through multiple mechanisms, providing a new strategy for the treatment of AS[89]. Another ApoA-I mimetic peptide ETC-642, is expected to lower manufacturing costs and improve scalability for rHDL production[90]. The researchers confirmed that the discoidal complexes of ETC-642 exhibit anti-inflammatory properties that are comparable to rHDL. These novel rHDL systems further expand the potential of biomimetic therapies, offering improved stability, functionality, and targeted cholesterol transport.

Beyond small-molecule drugs, rHDL has emerged as a promising platform for nucleic acid delivery. Jebari-Benslaiman et al.[91]

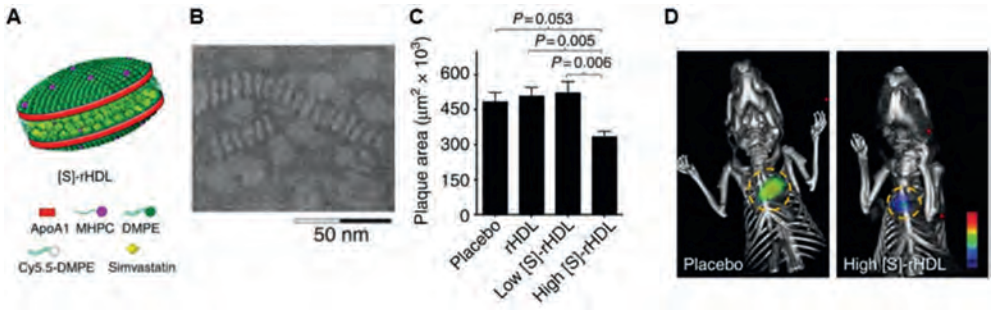

Figure 5 HDL delivery systems for AS treatment. (A) Schematic representation of [*S*]-rHDL. (B) Negative staining TEM images of [*S*]-rHDL. (C) High-dose [*S*]-rHDL-treated group exhibited the lowest plaque area compared with placebo, rHDL, and low-dose [*S*]-rHDL. (D) Fluorescence molecular tomography with computed tomography molecular imaging of protease activity demonstrated that high-dose [*S*]-rHDL treatment significantly decreased inflammation in the aortic roots of live *Apoe*$^{-/-}$ mice with advanced AS as compared with placebo. Reprinted with permission from Ref. 86. Copyright © 2014, Springer Nature Limited.

utilized rHDL to deliver microRNA for boosting cholesterol efflux from foam cells. The study demonstrates that HDL-mediated delivery of miRNAs to recipient cells depends on SR-B1. To note, there exists some evidence to prove the uptake of HDL cargo may occur through a non-endocytic pathway, which is highly desirable for drug delivery to protect nucleic acid drugs from lysosomal degradation[92,93]. Therefore, the potential of rHDL for nucleic acid delivery against AS holds great promise in the future.

3.2.2. LDL-based delivery systems

LDL, traditionally considered atherogenic due to its role in cholesterol deposition, has also been repurposed as drug delivery carriers[94]. The ligand−receptor interplay between LDL's structural apolipoprotein B (ApoB) moiety and low-density lipoprotein receptors (LDLR) enables targeted delivery of hypolipidemic compounds, inflammation-modulating therapeutics, and redox-regulating agents to vascular endothelial cells and lipid-laden macrophages[62,63]. Cholesteryl ester-enriched nanoparticles (LDE) demonstrate LDLR-mediated endocytotic uptake post-systemic administration[95]. The incorporation of drugs such as carmustine, paclitaxel, and dexamethasone into lipid core nanoparticles can effectively improve their anti-AS therapeutic effects[95-97]. In cholesterol-fed rabbits with induced AS, LDE−carmustine reduced lesion size by 90% compared to the controls[95]; Similarly, LDE−paclitaxel treatment resulted in a 60% reduction in atherosclerotic lesions and inhibited the infiltration of macrophages and smooth muscle cells into the intima[96].

A paradigm shift in AS treatment has also occurred with the exploration of lipoprotein-based vaccines. These adjuvant-vaccination strategies are primarily being actively developed to target ox-LDL and ApoB-containing lipoproteins, alleviating AS progression by promoting LDL clearance and reducing vascular inflammation[98]. Although still in early-stage research, lipoprotein-based nanovaccines offer a novel strategy for long-term cardiovascular protection.

3.3. EVs

EVs as naturally occurring lipid bilayer nanoparticles, share structural and functional parallels with engineered lipid-based nanosystems in drug delivery applications (Fig. 6A)[99]. These membrane-bound vesicles are endogenously secreted by diverse cell types and serve as multifaceted mediators of intercellular communication through their cargo of proteins, lipids, and nucleic acids[100]. As natural bioactive carriers, EVs exhibit diverse drug-loading capabilities, excellent biocompatibility[101], and tissue-targeting properties[102], making them important tools in AS treatment. Since the function of EVs is closely related to their origin[103], the EVs used for AS treatment mainly originated from cell types present at the plaque site, such as endothelial cells, smooth muscle cells, macrophages, and platelets. These exert therapeutic effects by leveraging their inherent regulatory contents against AS.

Endothelial dysfunction represents the first step in the pathogenesis of AS[104]. Early interventions targeting endothelial repair and aging represent a promising therapeutic approach. Endothelial cells, located on the inner surface of blood vessels, produce various factors to regulate vascular function. Therefore, endothelial cell-derived extracellular vesicles play a critical role in preserving vascular homeostasis. Studies have shown that exosomes derived from endothelial progenitor cells contain multiple miRNAs associated with AS inhibition, significantly reducing AS plaque formation and inflammatory factor production while restoring endothelial dysfunction in diabetic AS mouse models[105]. To mitigate endothelial dysfunction and preserve endothelial phenotype, Hergenreider et al.[106] reported that the transcription factor KLF2 induces endothelial cells to secrete EVs enriched with miR-143/145. These EVs transfer from endothelial cells to smooth muscle cells, modulating their phenotype and suppressing the expression of dedifferentiation-associated genes, ultimately reducing AS lesions in *Apoe*$^{-/-}$ mice.

In recent years, inflammation has been recognized as a key factor in AS progression[5]. Macrophages, as primary mediators of inflammatory responses, secrete exosomes with high inflammatory affinity and the ability to target inflamed sites[107]. Based on this, Wu et al.[108] developed an engineered exosome with pro-inflammatory targeting and anti-inflammatory properties. Using electroporation, they loaded the hexyl 5-aminolevulinate hydrochloride (HAL) molecule into M2 macrophage-derived exosomes (HAL@M2 Exo). HAL@M2 Exo specifically targeted inflamed regions *via* surface-expressed chemokine receptors, such as CCR2 and C−X−C Motif Chemokine Receptor 2 (CXCR2), and released anti-inflammatory cytokines. Moreover, the encapsulated HAL promoted heme biosynthesis and metabolism, generating anti-inflammatory compounds such as carbon monoxide and bilirubin. This therapeutic strategy demonstrated excellent anti-inflammatory effects in both *in vitro* and *in vivo* studies, significantly alleviating AS. Similarly, platelets, as

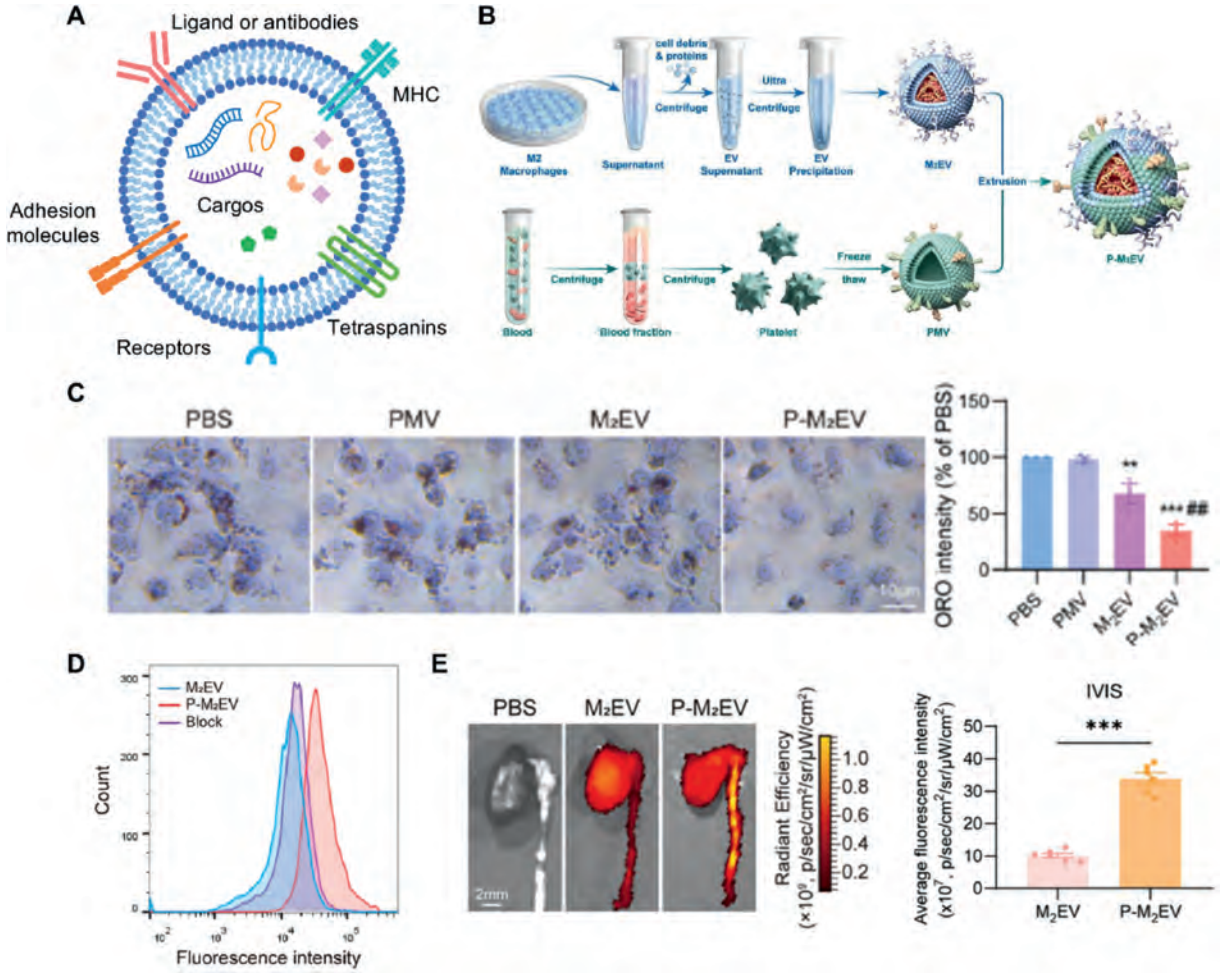

Figure 6 EVs for AS treatment. (A) Structure diagram of Extracellular Vesicles. (B) Schematic of vehicles for the fusion of M2 macrophage-derived extracellular vesicles with platelet membranes (P-M2EV). (C) Representative images and quantification of Oil Red O (ORO) staining in macrophages. (D) *In vitro* flow cytometric measurement of P-M2EVs' selective binding to activated macrophages through GPIb α-mediated recognition under oxidized LDL stimulation. (E) *In vivo* fluorescence tracking confirming atherosclerotic plaque-specific homing capacity of P-M2EVs in *Ldlr*$^{-/-}$ mice. (B—E) were reproduced with permission from Ref. 107 under the Creative Commons license.

immune-related cells, primarily contribute to thrombus formation following AS plaque rupture. Platelet-derived EVs (PLT-EVs) exhibit intrinsic affinity for inflamed sites and can serve as drug carriers for anti-inflammatory therapies[109]. Additionally, Xie et al.[107] designed a platelet-mimicking nanocarrier (P-M_2EV) by fusing platelet membranes with M2 macrophage-derived EVs (Fig. 6B). P-M_2EV exerted its therapeutic effects by releasing bioactive factors such as miR-99a-5p, effectively inhibiting foam cell formation and slowing AS progression (Fig. 6C)[107]. *In vitro* experiments and *in vivo* imaging demonstrated that the accumulation of P-M_2EV was significantly higher than that of other groups (Fig. 6D and E)[107].

Overall, EVs play an irreplaceable role in AS therapy. Their application in this field deserves deeper exploration. In the future, a wider variety of EVs from diverse cell types may be developed for AS treatment.

3.4. *Cell membrane-coated nanosystems*

Cell membrane-coated nanoparticles represent a distinct subclass of lipid-based nanosystems that integrate the natural lipid bilayer and membrane proteins of living cells onto synthetic cores. Unlike other lipid carriers such as liposomes or LNPs, these biomimetic systems retain the functional complexity of native cell membranes, enabling superior immune evasion, lesion-specific targeting, and prolonged systemic circulation. These features make them especially attractive for AS therapy, where immune modulation and precise plaque targeting are critical (Fig. 7A)[68].

3.4.1. *Red blood cell (RBC) and platelet membrane-coated nanosystems*

The RBC membrane is one of the most commonly used cellular membranes in membrane delivery systems for its "stealth" property and prolonged circulation benefiting from well-inherited biological characteristics[110]. Wang et al.[111] cloaked rapamycin-loaded poly(lactic-*co*-glycolic acid) nanoparticles with RBC membrane to evade the mononuclear phagocytic system clearance for AS treatment. Relying on the "do not eat me" CD47 protein, RBC membrane-cloaked nanoparticles achieved long blood circulation (Fig. 7B)[111] and thus facilitated the accumulation in atherosclerotic plaques, suggesting the potential of RBC membrane biomimetic nanoparticles as a feasible targeted delivery

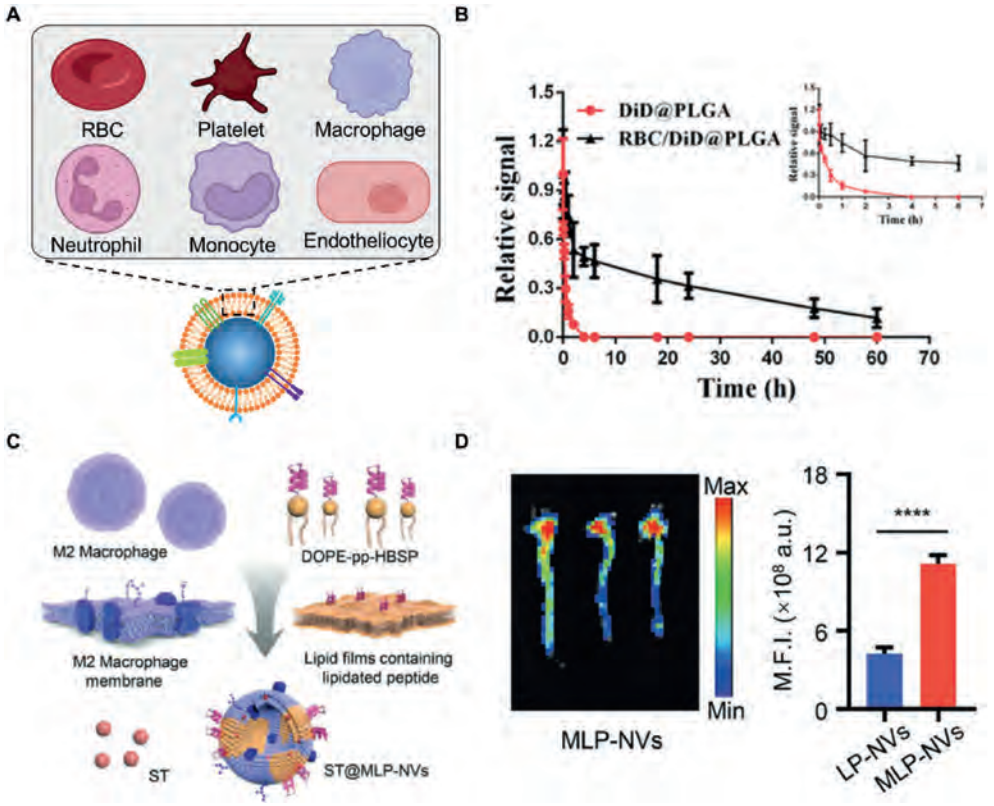

Figure 7 Cell membrane-coated nanosystems for AS treatment. (A) Different origins of cell membrane-coated nanosystems for AS treatments. (B) Pharmacokinetic studies of RBC/DiD@PLGA and DiD@PLGA in C57BL/6 mice. Reprinted with permission from Ref. 111. Copyright © 2019 The Authors. Published by WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (C) Schematic diagram of the preparation of MLP-NVs. (D) Representative fluorescence images of the whole aorta from *Apoe*$^{-/-}$ mice that received administration of DiD-loaded LP-NVs and MLP-NVs.

system for AS management[111]. Notably, the amphipathic nature of lipid constituents in cellular membranes, particularly phospholipids and cholesterol, confers unique physicochemical properties that facilitate structural modifications and membrane fusion processes. To further improve the targeting performance of RBC membrane, Zhong and associates[112] fabricated a "plug and play" functionalized RBC nanoplatform (RBC@DiD/CR_8), in which the CR_8 polypeptide was modified on the surface of the RBC membrane to actively target VCAM-1. RBC-coated nanoparticles exhibited favorable biocompatibility and low toxicity compared with free DTX. The *in/ex vivo* study demonstrated that the accumulation of RBC@DiD/CR8 in the atherosclerotic plaque regions was notably greater compared to RBC@DiD without the modification of the active targeting ligand. It has been reported that activated platelets target inflamed sites and interact with damaged vasculature *via* their membrane surface proteins, such as glycoprotein Ib, therefore increasing studies utilize the platelet membrane for the accurate localization of atherosclerotic plaques[113]. Song et al.[114] engineered a biomimetic drug delivery system through platelet membrane fusion technology (P-Lipo) for AS targeting. The hybrid biomimetic liposomes combined with platelet membranes can load therapeutic agents and, due to the inherent affinity of platelet membranes for damaged endothelium and plaque sites, efficiently accumulate at atherosclerotic lesions, maximizing therapeutic effect and minimizing off-target effects.

3.4.2. White blood cell membrane-coated nanosystems

As major cellular components of plaques, macrophages have proven to be an appealing source for biomimetic design[115]. The macrophage membrane can enhance the targeting efficiency of nanoparticles and their payload delivery to the lesion site, while also facilitating the scavenging of proinflammatory factors[116]. Guo et al.[117] used a macrophage membrane integrated with specially designed lipidated peptides for addressing multiple pathogenic factors in the complex plaque environment (Fig. 7C). *In vitro* and *in vivo* experiments demonstrated that the biomimetic macrophage membrane and lipidated peptide hybrid nanovesicles effectively accumulated in atherosclerotic plaques (Fig. 7D)[117], reducing the inflammatory level within the plaques and inhibiting the progression of AS. The study further revealed M2-polarized macrophages' superior therapeutic potential over naïve macrophages in inflammatory modulation, attributed to their distinct immunoregulatory functions within macrophage subtype polarization dynamics. Given the chronic inflammation in AS where immune cells play central roles, neutrophil membranes could also be engineered to carry anti-inflammatory drugs. Liu et al.[118] developed neutrophil-camouflaged ZIF-8 nanocarriers (AM@ZIF@NM) for precision delivery of miR-155 antisense oligonucleotides to activated endothelial cells in atherosclerotic lesions. Leveraging the CD18/ICAM-1 ligand−receptor axis, this platform significantly enhanced endothelial targeting efficiency

compared to non-coated counterparts. The AM@ZIF@NM NPs treatment yielded an effective inhibition of AS progression, with a plaque ratio of 6.77%.

Persistent monocytic infiltration constitutes a pivotal pathogenic event in nascent atheroma formation, driven by monocyte chemoattractant protein-1 that mediates leukocyte recruitment to inflamed arterial endothelium. Leveraging this natural tropism, engineered monocyte-derived vectors demonstrate enhanced plaque-penetrating capacity through chemokine receptor-mediated transendothelial migration, enabling precision delivery of therapeutic payloads to subendothelial microenvironments. In one study, the researchers demonstrated that monocyte membrane leverages monocyte-endothelium adhesive interactions to enhance the targeting to atheroprone vasculature and bypass healthy vasculature[119]. Monocyte cells membrane-coated nanosystem may provide a moderate method for penetrating through the fragile and unstable plaque to enhance the therapeutic effect while avoiding plaque rupture.

3.4.3. Other cell membrane-coated nanosystems

As discussed above, cell membrane-camouflaged nanoagents have been extensively used as cargo vesicles for the AS therapy, benefiting from inheriting the unique function of surface membrane proteins. However, the diversity of cell membrane types currently used in AS research is relatively limited when compared to the more extensive exploration observed in other diseases. Membranes derived from tumor cells, stem cells, fibroblasts, and bacteria have also been widely utilized to enhance targeting, penetration, or immune modulation[120-123]. While these membrane types have not been comprehensively investigated in AS, they may offer inspiration for future development. For example, growing evidence links gut microbiota to AS progression, suggesting a possible role for bacterial membrane-based delivery systems to modulate disease-related immune responses[124]. In another case, Li et al.[122] demonstrated that membranes derived from cancer-associated fibroblasts possess inherent targeting and penetration capabilities, indicating that vasculogenic fibroblast membranes may have application potential in AS.

Despite their promise, native membrane systems face intrinsic limitations in ligand−receptor pairing efficiency, constraining therapeutic targeting precision. To address this challenge, Zhong et al.[125] genetically modified endothelial cells to overexpress very late antigen-4 surface proteins using a mouse integrin alpha-4 lentiviral vector, thereby optimizing bioengineered endothelial cell membranes to improve active targeted therapy for AS. Another research group engineered RAW264.7 macrophage cells to overexpress MerTK and HEK293T cells to overexpress transferrin receptor (TfR), producing functional membranes for hybrid vesicle construction[126]. These hybrid membrane nanovesicles enhanced efferocytosis *via* MerTK and enabled magnetic targeting through TfR-mediated navigation. These studies suggest that genetically engineered cell membranes may not only broaden the available options of cell membrane origins but also expand the cell membrane functionality.

3.5. Intelligent lipid-based nanosystems

Intelligent drug delivery systems are developed to achieve spatiotemporally controlled drug release in response to endogenous (*e.g.*, pH, ROS, enzymes) or exogenous (*e.g.*, light, ultrasound) stimuli. By exploiting the pathophysiological hallmarks of atherosclerotic plaques, including localized acidosis, elevated ROS levels, and dynamic shear stress gradients, intelligent lipid-based nanosystems can be structurally tailored to confer microenvironment-responsive behaviors[127-129]. This biomimetic approach minimizes off-target effects while maximizing therapeutic precision at plaque sites[70].

The inherent versatility of lipid architectures enables the rational design of intelligent nanosystems through chemical modifications or hybrid formulations. Holme et al.[130] synthesized 1,3-diaminophospholipids and formulated them into nanovesicles with a lenticular morphology. These vesicles demonstrated stability under static conditions but exhibited content release upon exposure to elevated shear stress. The authors observed that the lenticular shape may contribute to instability along the vesicle's equator. Using a model cardiovascular system, they successfully demonstrated that these nanovesicles can selectively release their cargo in regions of high shear stress, highlighting their potential for treating AS. Zhou et al.[131] designed Rapa@TLNVs, a rapamycin-loaded biomimetic nanovesicle constructed by combining a ROS-sensitive thioketal phospholipid with macrophage membrane. Leveraging the inherent inflammatory tendencies of macrophage membranes and the ROS-activated properties of the thioketal linker, Rapa@TLNVs can effectively target plaque lesions and deliver rapamycin in a controlled manner, thereby synergistically mitigating inflammation. *In vivo* experiments using *Apoe*$^{-/-}$ mice demonstrated that Rapa@TLNVs administration significantly reduced lipid deposition, stabilized plaque structure, and attenuated the inflammatory response. Zhang et al.[132] designed a hyaluronan (HA)-anchored core−shell rHDL nanoparticle with a biodegradable poly(lactic-*co*-glycolic acid) (PLGA) core and ApoA-I covalently decorated on the lipid bilayer *via* HA anchoring. The HA coating provided enhanced stability and shielding, facilitating nanoparticle accumulation at leaky endothelial regions in atherosclerotic plaques with CD44 overexpression while minimizing liver uptake. Upon hyaluronidase-mediated degradation of the HA layer within atherosclerotic plaques, the retained ApoA-I enabled its targeted homing to immune macrophages. *In vitro* experiments showed HA-(C)−PLGA−rHDL exhibited significantly greater cholesterol efflux capacity compared to conventional rHDL (2.43-fold higher).

In addition to the direct synthesis of intelligent lipid materials, emerging strategies combine lipid nanostructures with non-lipid responsive components to create multifunctional therapeutic platforms. For example, Liu et al.[133] engineered a redox-sensitive nanodiagnostic platform integrating phosphatidylserine (PS)-targeting peptide motifs (TPCR) with ROS-responsive lipid-permeable probes, creating orientation-controlled theranostic assemblies (M-TPCR) through selective binding to inner-leaflet PS on activated macrophage membranes. This biomimetic system leverages macrophage membrane-derived stealth coatings to potentiate atherosclerotic lesion targeting, with fluorescence activation strictly contingent on concurrent ROS exposure and lipid microenvironment conditions. Another research synthesized nanoscale coordination polymers (NCPs) with a pH-responsive benzoic-imine linker (BI-linker) and Gadolinium (Gd^{3+}), creating a theranostic platform with dual imaging-therapeutic functionality[134]. To optimize biostability, PEGylated lipid bilayer NCPs were then used to modify NCPs. This NCPs-based pH-responsive dual-function nanomedicine enabled spontaneous MRI of plaques and efficacious treatment of AS. These intelligent lipid-based nanosystems leverage the biocompatibility and targeting capacity of lipid-based nanosystems while incorporating non-lipid materials with unique stimulus-sensing capabilities, achieving synergistic advantages.

Table 3 Summary of fabrication techniques of lipid-based nanosystems.

Preparation process	Advantage	Disadvantage	Application	Ref.
Microfluidics	Mild, simple to operate, rapid in preparation, high reproducibility, high stability and suitable for scaling up	High demands on equipment, and process parameters need to be optimized	LNPs; cell membrane-coated nanosystems	135,136
High-pressure homogenization	High stability and uniformity	Difficult to encapsulate sensitive drugs	SLNs; NLCs; LNEs	137
Thin film hydration	Simple to operate and facilitates the encapsulation of hydrophobic drugs	Difficult to encapsulate hydrophilic drugs and scale up	Liposomes; HDL-based delivery systems	86,138
Ethanol injection	Simple to operate	Poor uniformity, low reproducibility and limited encapsulation efficiency	LNPs; liposomes	135
Ultrasonic emulsification	Simple to operate, low cost and minimal use of organic solvents	Poor stability, low uniformity and difficult to scale up	LNEs	137
Reverse-phase evaporation	Facilitates the encapsulation of hydrophobic drugs	Extensive use of organic solvents, poor uniformity, difficult to operate and scale up	Liposomes	138
Emulsion diffusion method	Simple to operate, high encapsulation efficiency and uniformity	Need to select the appropriate solvent and difficult to scale up	LNMs	139

LNPs, lipid nanoparticles; SLNs, solid lipid nanoparticles; NLCs, nanostructured lipid carriers; LNEs, lipid-based nanoemulsions; HDL, high density lipoprotein; LNMs, lipid-based nanomicelles.

4. Fabrication techniques

Lipid-based nanosystems share a fundamental composition of lipid-based materials, which results in similar preparation methodologies across different types despite structural variations. Currently, several common synthesis techniques for lipid nanocarriers are presented in Table 3[86,135-139]. Balancing safety, therapeutic efficacy, batch homogeneity, and scalability remains a pivotal consideration in their development—a prerequisite for clinical translation of lipid-based delivery systems. Microfluidics employs micron-scale channels to precisely regulate the mixing ratio between lipid−ethanol and aqueous phases, utilizing turbulence for nanoparticle self-assembly[136]. This method enables continuous production of monodisperse LNPs with uniform size (PDI<0.2) and >90% encapsulation efficiency, particularly suited for mRNA vaccines[135,136]. High-pressure homogenization (100−1500 bar) fragments lipid aggregates *via* shear forces, with hot homogenization for industrial-scale production (*e.g.*, Doxil®) and cold homogenization to minimize thermal degradation of sensitive drugs[137]. Thin film hydration involves lipid film formation by rotary evaporation followed by hydration and extrusion, a classical laboratory method for multilamellar vesicles that supports pH-gradient-driven active drug loading[86,138]. Ethanol injection rapidly introduces lipid ethanol solution into aqueous media to drive self-assembly, offering mild conditions but requiring ethanol residue control[135]. Ultrasonic emulsification applies cavitation (20−40 kHz) to reduce particle size, often combined with other methods, yet risks metal contamination[137]. Reverse-phase evaporation forms large unilamellar vesicles *via* emulsion-solvent evaporation, ideal for hydrophilic drugs (60%−80% encapsulation)[138]. Emulsion diffusion leverages semi-polar solvent diffusion to precipitate lipids, suitable for hydrophobic drugs but requiring solvent optimization[139].

5. Clinical translation development

Current clinical strategies for the treatment of AS primarily rely on a combination of lipid-lowering agents, antiplatelet therapies, antihypertensive drugs, and antidiabetic medications[6]. Statins remain the first-line therapy due to their robust LDL-lowering capacity and well-documented reduction in cardiovascular events[140]; however, their pleiotropic anti-inflammatory effects are often limited by poor bioavailability at the plaque site and dose-dependent adverse effects[141,142]. PCSK9 inhibitors offer an effective add-on therapy, especially in patients with familial hypercholesterolemia or statin intolerance, though their high cost and injectable administration limit widespread use[143]. Antiplatelet agents like aspirin and $P2Y_{12}$ inhibitors are essential in preventing thrombotic complications but carry an increased risk of bleeding[144]. Antihypertensives and antidiabetic drugs contribute to vascular stabilization and metabolic control, yet their use is restricted by systemic side effects and suboptimal plaque targeting[145,146]. Collectively, these therapies focus predominantly on symptom management and risk reduction, with limited capacity to directly reverse plaque pathology.

Lipid-based nanosystems have demonstrated significant potential in improving the bioavailability and specificity of therapeutic agents[147,148]. As of the latest data, over 2400 interventional studies are listed on ClinicalTrials.gov, utilizing lipid-based

Table 4 The clinical trials of lipid-based nanosystems for AS treatment.

Type	NCT Number	Phase	Starting date	Condition	Intervention	Sponsor	Ref.
Liposome	NCT04197323	Phase 2	2019-10-01	Peripheral artery disease	Drug: Alprostadil liposomes	CSPC ZhongQi pharmaceutical technology co., Ltd.	149
Liposome	NCT01601106	Phase 1 Phase 2	2011-09-01	AS, inflammation	Drug: Liposomal prednisolone, Drug: Placebo	Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	150
Liposome	NCT01647685	Phase 1 Phase 2	2012-05-01	AS	Drug: Nanocort Drug: Methylprednisolone Drug: Placebo	Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	151
Liposome	NCT00053716	Phase 2	2003-02-01	Peripheral vascular disease	Drug: Liprostin (liposomal prostaglandin E1)	Endovasc	152
Liposome	NCT05992896	Phase 4	2023-09-06	Peripheral arterial disease	Drug: Bupivacaine liposomes, Drug: Placebo	Mayo clinic health system-Eau Claire, Eau Claire, Wisconsin, United States	153
LDL-like nanoparticles	NCT04148833	Phase2 Phase 3	2019-06-23	AS	Drug: LDE-paclitaxel Drug: LDE-placebo	University of Sao Paulo general Hospital	154
LDL-like nanoparticles	NCT04616872	Phase2 Phase 3	2020-10-10	AS	Drug: Methotrexate-LDE Drug: Placebo-LDE	University of Sao Paulo general Hospital	155

AS, atherosclerosis; LDL, low density lipoprotein; LDE, cholesteryl ester-enriched nanoparticles.

nanosystems as drug delivery carriers for a wide array of active pharmaceutical ingredients. These studies address a variety of diseases, including multiple types of cancer, virus infection, and pain management. However, clinical trials of lipid nanocarriers specifically targeting AS treatment remain relatively limited, as detailed in Table 4[149-155]. Currently, liposomes are the most widely used lipid nanocarriers in clinical trials for the treatment of AS. Nanocort is a novel intravenous formulation composed of pegylated liposomes encapsulating prednisolone sodium phosphate. The lipid bilayer consists of distearoylphosphatidylcholine, distearoylphosphatidylglycerol, cholesterol, and polyethylene glycol−conjugated distearoylphosphatidyl-ethanolamine[156]. It is designed for the targeted treatment of inflammatory diseases such as AS and rheumatoid arthritis. The SILENCE trial[150], a Phase I/II study registered under NCT01601106, focuses on the use of Nanocort in patients at risk for atherosclerotic disease. This single-center, randomized, placebo-controlled trial aims to assess the therapeutic efficacy of intravenously administered Nanocort in individuals with severe inflammation in the carotid or aortic AS plaques. Participants are randomized to receive either liposomal prednisolone or placebo, with the primary outcome measure assessed *via* ^{18}Fludeoxyglucose positron emission computed tomography scan (^{18}FDG PET-CT scan) on Days 8−13. The trial aims to determine the impact of Nanocort on inflammation, potentially offering a novel approach to atherosclerotic plaque management.

LDL-mimetic nanoparticles have entered clinical investigation for atherosclerotic cardiovascular disease. A prospective randomized double-masked trial[157] evaluated cholesterol-rich nanoemulsions loaded with antiproliferative paclitaxel (PTX-LDE) in patients with stable multivessel coronary artery disease under optimized medical therapy. Participants received six intravenous infusions (175 mg/m^2 PTX-LDE *vs.* placebo nanoemulsions) at 21-day intervals. Primary endpoints were assessed through coronary/aortic computed tomography angiography performed 1−4 weeks post-randomization and 3−8 weeks after final treatment. Safety evaluations included serial biochemical profiling (alanine aminotransferase, aspartate transaminase, bilirubin) and clinical monitoring every 3 weeks. Results demonstrated no treatment-related toxicities across both cohorts. The PTX-LDE group exhibited non-significant reductions in IL-6 (∼16%) and hs-CRP (∼28%) compared to baseline, with placebo showing minimal biomarker fluctuations. Plaque progression analysis revealed comparable changes between groups, with no statistically significant differences in total plaque volume. The trial confirmed the safety profile of LDE-paclitaxel while suggesting potential anti-inflammatory effects meriting extended clinical evaluation. CER-001[158-160], an HDL mimetic composed of recombinant human ApoA-I complexed with phospholipids, specifically sphingomyelin and dipalmitoylphosphatidylglycerol. CER-001 is designed to mimic the structure and function of natural HDL particles. Phase I clinical trials have demonstrated that CER-001 is well-tolerated at doses up to 45 mg/kg, with no significant adverse effects reported. Additionally, EVs have been demonstrated in trials to play an indispensable role in the development of AS[161].

Nowadays, most clinical trials utilize traditional nanosystems (*e.g.*, liposomes), while more multifunctional advanced systems for the treatment of AS remain at preclinical stages due to various challenges. The following section discusses the current challenges and future opportunities in advancing lipid-based nanosystems toward clinical translation.

6. Challenges and opportunities

6.1. Challenges

Lipid nanocarriers outperform traditional delivery systems by extending drug half-life, making them ideal for treating chronic diseases like AS[162]. They can also encapsulate a broader range of drugs, including nucleic acids, enabling multi-target therapy[163]. Over the past 20 years, with deeper insights into AS and advancements in nanotechnology, more modified lipid nanocarriers have been used for treatment at various stages of AS. However, few have reached clinical stages due to significant developmental challenges. The predominant challenges can be encapsulated as follows.

Delivery efficiency: The delivery efficiency of lipid nanocarriers has long been one of the main issues limiting their development. In the treatment of AS, the delivery efficiency of carriers is related to their circulation time in the bloodstream, their extravasation ability through damaged vascular endothelium, and their distribution within plaques[3]. Additionally, the size, surface charge, shape, rigidity, chemical composition, and surface modification of the carriers all affect their delivery efficiency[164]. When delivering nucleic acid drugs, the endosomal escape capability of the carriers also greatly impacts delivery efficiency[165]. Additionally, the reticuloendothelial system, particularly the liver and spleen, rapidly sequesters lipid carriers, reducing extrahepatic delivery efficiency. A case in point is conventional LNPs (*e.g.*, those formulated with DLinDMA), which show over 50% of the injected dose accumulates in the liver within just half an hour after administration[166]. Therefore, systematically improving the delivery efficiency of carriers is a key step in promoting their development.

Safety concerns: Although lipid nanocarriers have already demonstrated certain advantages in biocompatibility compared to other traditional carriers (such as polymeric nanoparticles, metal nanoparticles, etc.), there are still some safety concerns. Ferraresso et al.[167] observed a significantly higher level of alanine transaminase in serum in mice treated with siLuc-ALC-0315, suggesting the potential hepatotoxicity of ionizable cationic lipids. PEGylated liposomes have been reported to activate the complement system in some patients, triggering pseudoallergic reactions known as complement activation-related pseudoallergy[168]. For AS therapy, the unique microenvironment at the site of atherosclerotic plaques[169], which results in a lack of specificity for material targeting to the plaques, thereby causing off-target effects and safety hazards. Therefore, further enhancing the specificity of carriers for targeting plaques is expected to improve their safety and thus promote the clinical translation of lipid-based nanocarriers for AS treatment.

The atherosclerotic animal model: Lipid nanocarriers show promise in treating AS, but their efficacy in humans needs further validation[170]. Currently, research on AS primarily utilizes animal models, including mice, rats, and rabbits[171]. Among these, mice have become the most widely used animals for studying AS due to their well-defined genetics, ease of breeding, and availability of numerous transgenic strains. To date, the Jackson Laboratory lists over 200 strains suitable for AS research, with *Apoe*$^{-/-}$, *Ldlr*$^{-/-}$, and human ApoB-100 transgenic mice being the most popular. However, translating results from these animal models to human patients is challenging due to significant differences in AS pathobiology[172]. For instance, *Apoe*$^{-/-}$ mice model typically has no human-like lipid profile and no spontaneous plaque rupture, thrombosis, and complications[173]. Therefore, making animal models more clinically relevant is a key challenge in AS treatment research.

To overcome multifaceted barriers in the clinical translation of lipid-based nanosystems for AS, future strategies must integrate both disease-specific barriers and the unique physicochemical attributes of lipid materials. Basically, deciphering the structure-activity relationships of lipid-based nanosystems in AS-specific conditions will facilitate the design of systems optimized for plaque penetration, immune modulation, and gene silencing. Additionally, a deeper understanding of how lipid-based nanosystems interact with the plaque microenvironment at the molecular and cellular levels will provide actionable insights for improving delivery precision and functional outcomes. The integration of real-time imaging technologies to track *in vivo* biodistribution and therapeutic behavior of lipid-based nanosystems will aid in assessing efficacy, minimizing off-target effects, and personalizing treatment strategies. Furthermore, to address the translational gap posed by current animal models, the adoption of large animal models, humanized immune systems, and organ-on-a-chip microphysiological platforms may better replicate the human vascular and immune milieu, facilitating more predictive preclinical evaluations. Together, these interdisciplinary approaches are expected to accelerate the safe and effective clinical translation of lipid-based nanosystems for AS.

6.2. Future opportunities

Currently, with the continuous development of lipid nanocarriers and the deepening understanding of the pathobiology of AS, new requirements have been put forward for lipid nanocarriers used in the treatment of AS. Therefore, these carriers for the treatment of AS in the future must be sufficiently flexible and comprehensive to address the diverse etiological factors of AS. The followings are some promising therapeutic strategies.

Multi-strategy combined therapies: Given the complexity of AS etiology, monotherapy often fails to achieve satisfactory therapeutic outcomes[174,175]. Leveraging the potent delivery capabilities of lipid-based nanocarriers, emerging therapeutic agents hold great promise for exerting significant therapeutic effects against AS. For instance, lipid-based nanosystems may offer a feasible strategy to deliver gene-editing tools or proteolysis-targeting chimera (PROTAC) drugs to repair the underlying pathology rather than merely alleviate symptoms. Additionally, an increasing number of studies are focusing on the rational design of lipid materials[176,177]. By tailoring these materials to align with the pathological features of AS—incorporating targeting capabilities and biological functionalities—it is anticipated that their integration with novel therapeutic agents will further enhance therapeutic efficacy.

Theranostics: One of the key clinical challenges in AS lies in its asymptomatic progression and the sudden occurrence of fatal plaque rupture. Current treatment often fails to intervene at the optimal window due to the lack of early-stage diagnostics. Common diagnostic approaches for AS, such as coronary angiography, MRI, PET, and CT imaging, remain limited in their capacity for early plaque identification and vulnerability assessment[178]. In this context, lipid-based nanosystems have emerged as a highly promising solution for integrating diagnosis and therapy in AS management. The lipophilic and biomimetic nature of lipid-based nanocarriers may confer unique advantages in terms of sensitivity, specificity, and deep tissue penetration for

the diagnosis of atherosclerotic plaque. Moreover, these systems can be functionalized with disease-specific biomarkers (*e.g.*, VCAM-1, lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1)) to achieve precise targeting and controlled release of therapeutics. Their intrinsic compatibility with both diagnostic tracers and therapeutic payloads enables real-time monitoring and synchronized treatment. This dual functionality not only supports early diagnosis and disease staging but also allows for dynamic assessment of therapeutic response, making them a transformative tool for non-invasive, personalized AS management.

Anti-AS Vaccine: The concept of preventing or treating AS through vaccination emerged as early as the 1990s[179,180]. The delivery of antigens related to the development of AS, such as derivatives of Apo-B and LDL[181,182], or the selective inhibition of inflammation at the plaque site[183], holds promise for the prevention of AS. These processes may be associated with the activation of regulatory T cells[184,185]. However, the development of vaccines targeting self-antigens must avoid potential dangers and long-term adverse reactions. Lipid nanocarriers, known for their high stability, biocompatibility, and efficient delivery, have become an ideal choice for vaccine delivery. Therefore, with the further development of lipid nanocarriers, they may be applied to the preparation of anti-AS vaccines to prevent this disease.

7. Conclusions

AS persists as a formidable worldwide healthcare burden, compelling the sustained pursuit of innovative therapeutic strategies. This review has provided an in-depth overview of lipid-based nanosystems for AS treatment, highlighting their evolving approaches. Traditional lipid-based delivery systems like liposomes, SLNs, NLCs, LNEs, and LNMs have laid the foundational groundwork for this field. However, recent advancements have focused on more sophisticated platforms and novel therapeutic strategies to address the complex and heterogeneous nature of the disease, therefore facilitating the development of diverse advanced lipid-based nanosystems. Clinical translation of lipid nanocarriers faces obstacles related to delivery efficiency, safety concerns, and differences between animal models and human pathobiology. Future opportunities lie in the development of multi-strategy combined therapies, theranostics, and anti-AS vaccines to address the complex plaque microenvironment. In conclusion, lipid-based nanosystems hold significant promise for the future of AS treatment. Continued research and innovation are crucial to address the current challenges and fully realize their potential, ultimately improving patient outcomes and reducing the global burden of this chronic and life-threatening disease.

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Author contributions

Xinxin Zhang, Xiangrong Song, Lijun Li, and Mengran Guo conceived the manuscript. Lijun Li, Mengran Guo, Zhangyu Wang, Mingxuan Yu, Dian Cai, and Yuqi Xu summarized the literatures and wrote the manuscript. Lijun Li, Mengran Guo, Mingxuan Yu, Dian Cai, Yuqi Xu, Zhi Liu, Can Huang, Zhaohui Jin, and Yongmei Xie prepared the figures and tables. Lijun Li, Mengran Guo, Zhangyu Wang, Xiangrong Song, and Xinxin Zhang revised the manuscript. Xinxin Zhang and Xiangrong Song were responsible for supervision. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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