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Review Article

# Nanoparticle-Based Drug Delivery for Cardiovascular Therapeutics: Recent Advances and Clinical Translation

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**ABSTRACT**

Cardiovascular Diseases (CVDs) remain the leading cause of death worldwide, and conventional pharmacotherapy for atherosclerosis, myocardial infarction, hypertension, thrombosis, and dyslipidaemia is still constrained by poor aqueous solubility, non-specific biodistribution, short circulation half-life, and off-target toxicity. Nanocarriers can address these limitations through site-specific accumulation, controlled release, and protection of labile payloads such as nucleic acids and peptides. This narrative review provides an indication-based and platform-by-platform critical appraisal of lipid-based, polymeric, micellar, inorganic, and biomimetic nanocarriers, together with ligand-conjugated siRNA and extracellular vesicles as closely related delivery systems, weighing the advantages, limitations, and clinical readiness of each. Clinical translation is examined in detail, covering the approved and late-stage RNA-interference therapeutics inclisiran, vutrisiran, and patisiran, the ongoing ORION-4 outcomes trial, first-in-human lipid-nanoparticle gene editing, polymer-coated stents, and the largely negative or absent clinical evidence for plaque-targeted particulate carriers. A central conclusion is that cardiovascular nanomedicine has so far reached patients almost exclusively through hepatocyte-directed RNA delivery, whereas the much larger preclinical literature on plaque-, myocardium-, and thrombus-targeted carriers has not yet been validated in outcome-driven trials. Barriers relating to scale-up, immunogenicity, targeting efficiency in humans, and regulation are discussed, and emerging directions, namely artificial-intelligence-assisted formulation design, extracellular-vesicle carriers, lipid-nanoparticle gene editing, and precision nanomedicine, are evaluated together with the prerequisites each must meet before clinical use.

**Keywords:** Atherosclerosis, Cardiovascular disease, Drug delivery, Extracellular vesicles, GalNAc, Lipid nanoparticles, Nanoparticles, Precision nanomedicine, siRNA, Theranostics.

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## INTRODUCTION

Cardiovascular Diseases (CVDs), encompassing atherosclerosis, coronary artery disease, myocardial infarction, heart failure, hypertension, and thromboembolic disorders, remain the largest cause of global mortality, with the World Heart Federation estimating approximately 20 million CVD deaths in 2021.[1] Despite considerable progress with statins, antiplatelet agents, antihypertensives, and anticoagulants, conventional oral and parenteral formulations of these drugs are frequently limited by poor aqueous solubility, rapid systemic clearance, non-specific tissue distribution, and dose-limiting adverse effects such as bleeding, myopathy, and hepatotoxicity.[2] These pharmacokinetic and safety constraints have sustained interest in nanotechnology-enabled drug delivery as a means of improving the therapeutic index of both established and emerging cardiovascular agents.

Nanoparticles (NPs) for drug delivery are colloidal carriers, typically tens to a few hundred nanometres in diameter, although regulatory definitions extend to 1000 nm where size-dependent properties are relevant.[3] They combine a high surface-area-to-volume ratio and tunable surface chemistry with the capacity to encapsulate or conjugate small molecules, peptides, proteins, and nucleic acids.[4,5] Surface functionalisation with ligands directed against receptors overexpressed on activated endothelium, monocytes/macrophages, or platelets enables active targeting, while stimuli-responsive designs release their payload in response to local pH, Reactive Oxygen Species (ROS), enzymatic activity, shear stress, or externally applied magnetic or thermal energy.[5]

In vascular disease, nanoscale carriers may extravasate preferentially through the leaky, inflamed endothelium of atherosclerotic plaques and infarcted myocardium, an effect conceptually analogous to the Enhanced Permeability and Retention (EPR) phenomenon first described in tumours.[6,7] This analogy should

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be treated with caution: even in tumours, nanoparticle accumulation is heterogeneous and frequently modest,[8] and equivalent quantitative evidence in human atherosclerotic lesions is sparse. Whether passive accumulation alone can deliver therapeutically meaningful doses to plaque or myocardium is therefore an open question that recurs throughout this review.

## Positioning of this review and how it differs from previous reviews

Several recent reviews have addressed nanoparticle-based cardiovascular drug delivery, but from comparatively narrow perspectives. Yang *et al.* provided a broad, largely descriptive survey of nanoparticle platforms for cardiovascular disease without a systematic weighing of platform-specific clinical readiness.[2] Jha *et al.* emphasised recent preclinical advances across indications but did not critically compare the translational trade-offs between platforms or address computational design strategies.[4] Beg *et al.* and Patel *et al.* focused predominantly on the mechanistic rationale for nanoparticle-mediated delivery, with limited discussion of regulatory status or landmark clinical-trial outcomes.[9,10] Most recently, Saadh *et al.* summarised advances in nanostructured cardiovascular delivery systems.[11] but, to the best of our knowledge, did not integrate the latest clinical-trial evidence with the convergence of Artificial-Intelligence (AI)-guided formulation design, Extracellular-Vesicle (EV)-based carriers, and precision nanomedicine that is now reshaping the field.

The present review differs from these antecedents in four respects:

### Critical comparison

It couples a platform-by-platform appraisal of advantages, limitations, and clinical readiness (Tables 1 and 2; Figure 1) with an indication-based synthesis (Figure 2), rather than presenting either in isolation.

### Expanded clinical translation

It gives a structured account of approved and late-stage RNA therapeutics (inclisiran, vutrisiran, patisiran), the ORION-4 outcomes trial, first-in-human lipid-nanoparticle gene editing, device-based polymer delivery, early clinical experience with plaque-targeted carriers, and regulatory status (Table 3; Figure 3).

### Conceptual clarity

It distinguishes true particulate carriers (lipid nanoparticles) from ligand-conjugated siRNA, two platforms that are often conflated but differ in delivery mechanism and in what their clinical success implies for the wider field.

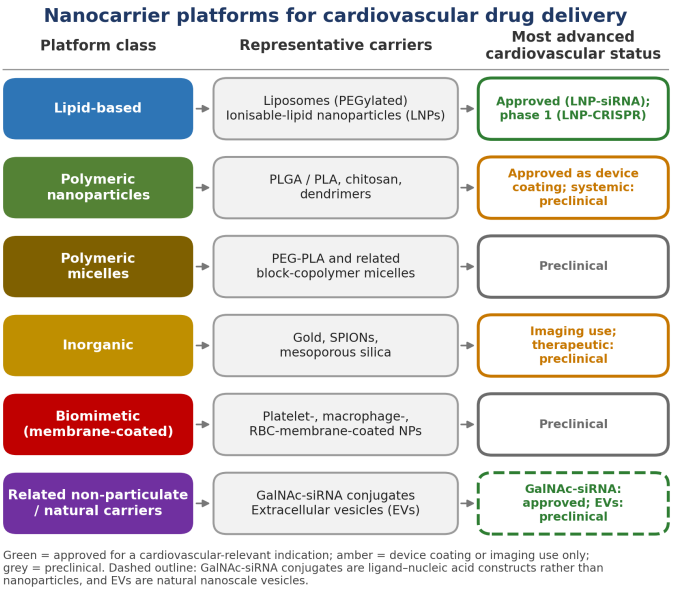



**Figure 1:** Classification of principal nanocarrier platforms investigated for cardiovascular drug delivery, with the most advanced cardiovascular status of each. GalNAc, N-acetylgalactosamine; LNP, lipid nanoparticle; PLGA, poly(lactic-co-glycolic acid); PLA, polylactic acid; SPION, superparamagnetic iron oxide nanoparticle; RBC, red blood cell; EV, extracellular vesicle.

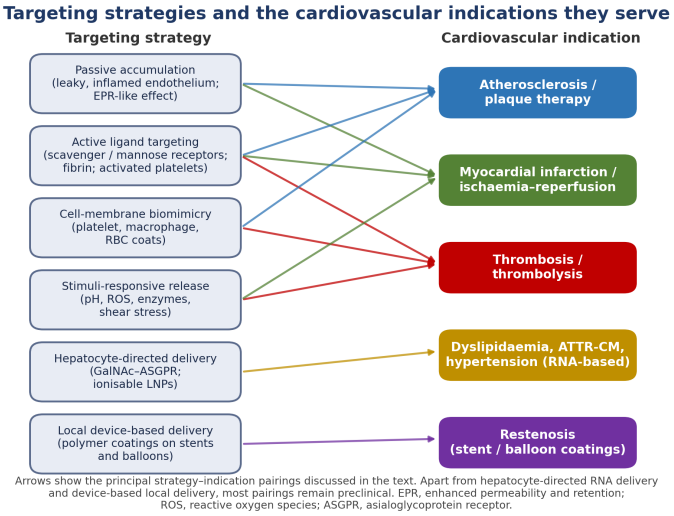



**Figure 2:** Nanocarrier targeting strategies and the principal cardiovascular indications they serve. EPR, enhanced permeability and retention; ROS, reactive oxygen species; ASGPR, asialoglycoprotein receptor.

## Evidence-graded future directions

It evaluates AI-assisted nanoparticle design, EV-based carriers, lipid-nanoparticle gene editing, and precision nanomedicine, together with the prerequisites each must meet before clinical use (Table 4 and Figure 4).

Building on this rationale, the review aims to provide an integrated and critically comparative overview of the principal classes of cardiovascular nanocarriers, their mechanistic rationale, representative preclinical and clinical evidence across major

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**Table 1: Principal nanocarrier platforms used in cardiovascular drug delivery and their key characteristics.**

| Platform class | Representative carriers | Key advantages | Principal cardiovascular application |
|---|---|---|---|
| Liposomes / lipid nanoparticles | PEGylated liposomes, ionisable-lipid LNPs | Biocompatible; encapsulate hydrophilic and lipophilic drugs; deliver nucleic acids | Anti-inflammatory plaque therapy (preclinical/early clinical); siRNA/mRNA and gene-editing delivery (e.g., TTR silencing, ANGPTL3 editing) |
| Polymeric nanoparticles | PLGA, PLA, chitosan, dendrimers | Tunable degradation, sustained release, surface functionalisation | Restenosis prevention, drug-eluting stent and balloon coatings (device-based use); systemic anti-proliferative therapy (preclinical) |
| Polymeric micelles | PEG-PLA / block-copolymer micelles | Small size, high solubilisation capacity for poorly water-soluble drugs | Solubilisation of poorly soluble agents such as statins (preclinical) |
| Inorganic nanoparticles | Gold, iron oxide (SPION), mesoporous silica | High stability, intrinsic imaging contrast, photothermal/magnetic responsiveness | Theranostic plaque imaging, image-guided therapy, MRI contrast |
| Biomimetic / cell-membrane-coated NPs | Platelet-, macrophage-, RBC-membrane-coated NPs | Prolonged circulation, immune evasion, natural affinity for injured vasculature | Targeted thrombus and plaque homing, reduced opsonisation (preclinical) |
| Ligand-conjugated siRNA (non-particulate benchmark) | GalNAc-siRNA (inclisiran, vutrisiran) | Receptor-mediated hepatocyte uptake; subcutaneous dosing at 3-6-month intervals | PCSK9 silencing for LDL-C lowering; TTR silencing in ATTR-CM |
| Extracellular vesicles (emerging) | Exosomes, microvesicles, engineered EVs | Natural surface antigens, low intrinsic immunogenicity, intercellular cargo transfer | Cardiac repair, anti-inflammatory and pro-angiogenic delivery (preclinical) |

Abbreviations: ANGPTL3, angiopoietin-like protein 3; ATTR-CM, transthyretin amyloid cardiomyopathy; EVs, extracellular vesicles; GalNAc, N-acetylgalactosamine; LDL-C, low-density lipoprotein cholesterol; LNPs, lipid nanoparticles; MRI, magnetic resonance imaging; NPs, nanoparticles; PCSK9, proprotein convertase subtilisin/kexin type 9; PEG-PLA, polyethylene glycol-polylactic acid; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); RBC, red blood cell; siRNA, small interfering ribonucleic acid; SPION, superparamagnetic iron oxide nanoparticle; TTR, transthyretin.

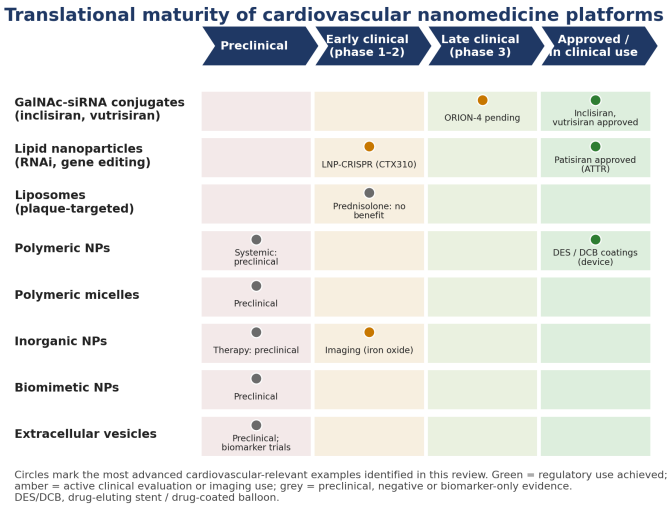



**Figure 3:** Translational maturity of cardiovascular nanomedicine platforms. DES/DCB, drug-eluting stent / drug-coated balloon.

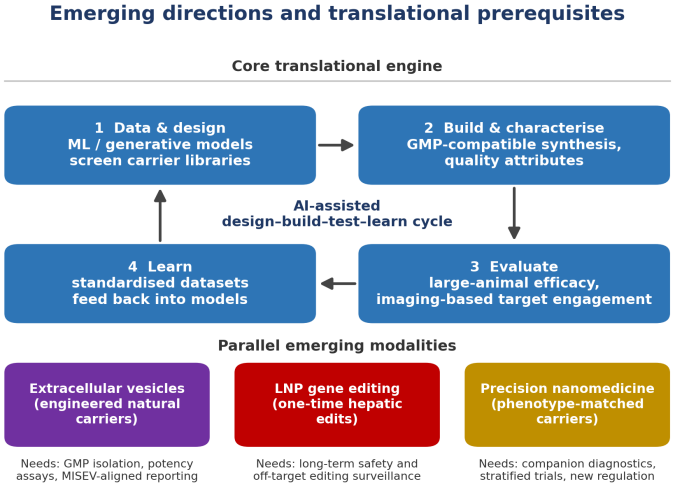



**Figure 4:** Emerging directions in cardiovascular nanomedicine and the prerequisites for clinical translation. GMP, Good Manufacturing Practice; MISEV, Minimal Information for Studies of Extracellular Vesicles.

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cardiovascular indications, and the translational challenges that continue to limit widespread clinical adoption.

## METHODOLOGY

This article is a narrative review. A structured literature search was performed across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for articles published between January 2015 and February 2026, with emphasis on publications from 2023 onward to capture the most recent advances. Clinical-trial registries (ClinicalTrials.gov) and regulatory sources (US FDA and Indian DBT/ICMR/CDSCO documents) were consulted for trial status and approvals, and clinical and regulatory information was updated in September 2026. Search terms, used singly and in combination, included: "nanoparticle*", "drug delivery", "cardiovascular disease", "atherosclerosis", "myocardial infarction", "thrombosis", "theranostic", "lipid nanoparticle", "siRNA", "GalNAc", "inclisiran", "vutrisiran", "patisiran", "clinical trial", "regulatory", "extracellular vesicle", "artificial intelligence", and "biomimetic nanoparticle".

Peer-reviewed original research articles, systematic and narrative reviews, and clinical trial reports published in English were considered for inclusion. Landmark clinical investigations (phase 2 and 3 trials and cardiovascular outcome trials) and high-impact original studies were prioritised for platform-specific claims, with reviews used mainly for orientation. Conference abstracts without accompanying full-text articles, non-peer-reviewed preprints, and studies not related to a cardiovascular indication were excluded. Reference lists of retrieved articles were additionally hand-searched. Given the narrative nature of this review, no formal risk-of-bias assessment or meta-analytic synthesis was undertaken; findings are synthesized qualitatively by nanoparticle platform and clinical indication, and evidence that is exclusively preclinical is identified as such.

## Classification Of Nanoparticle Platforms Used In Cardiovascular Therapeutics

Nanocarriers explored for cardiovascular applications are broadly classified as lipid-based, polymeric, inorganic, and biomimetic systems, with polymeric micelles usually considered a distinct self-assembled subclass; each offers a distinct balance of drug-loading capacity, biodegradability, circulation time, and manufacturing complexity.[10] Figure 1 presents this classification together with two closely related modalities that are not nanoparticles in the strict sense but are essential for interpreting the clinical literature: ligand-conjugated (GalNAc) siRNA and extracellular vesicles. Table 1 summarises representative carriers, advantages, and principal applications, and Table 2 gives a critical side-by-side appraisal of advantages, limitations, and translational status. The tables are placed at the end of this manuscript, following the reference list.

## Lipid-based nanoparticles

Liposomes, composed of one or more phospholipid bilayers surrounding an aqueous core, are among the most clinically mature nanocarriers owing to their biocompatibility and capacity to encapsulate both hydrophilic and lipophilic drugs.[10] PEGylation of the liposomal surface extends systemic circulation by reducing opsonisation and reticuloendothelial clearance, thereby increasing accumulation at inflamed vascular sites. Their cardiovascular record is nevertheless instructive: liposomes have been shown to reach human plaque macrophages, yet the first clinical test of a plaque-targeted liposomal glucocorticoid did not reduce vascular inflammation.[12] (see Clinical translation).

Ionisable-Lipid Nanoparticles (LNPs), refined during the development of messenger ribonucleic acid (mRNA) vaccines, protect labile nucleic acids from nuclease degradation and promote endosomal escape after cellular uptake.[13] Patisiran, a small interfering ribonucleic acid (siRNA) against hepatic transthyretin (TTR) formulated in an LNP for intravenous infusion, was the first siRNA therapeutic to be approved.[14] An earlier LNP formulation of PCSK9-directed siRNA (ALN-PCS, an intravenous candidate) provided proof of concept in a phase 1 trial, lowering circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) and low-density lipoprotein cholesterol (LDL-C) after a single dose.[15] More recently, LNPs have delivered CRISPR-Cas9 and base-editing payloads to the liver in non-human primates and in patients,[16,17] as discussed under dyslipidaemia below.

Critically, LNPs offer the most mature manufacturing base and the strongest regulatory precedent among particulate carriers. Their applicability outside hepatocyte-directed RNA delivery is nevertheless constrained by near-obligate hepatic tropism, anti-PEG immunogenicity on repeated administration, and the cost and cold-chain requirements of GMP-grade ionisable-lipid synthesis.[5,11,13] Extra-hepatic LNP delivery to plaque, myocardium, or thrombus has not yet been achieved clinically.

## Ligand-conjugated siRNA (GalNAc-siRNA): a non-particulate clinical benchmark

Inclisiran and vutrisiran are frequently described as nanoparticle therapeutics, but they are not. Each is a chemically stabilized siRNA covalently conjugated to a triantennary N-acetylgalactosamine (GalNAc) ligand that binds the hepatocyte asialoglycoprotein receptor (ASGPR), which mediates receptor-dependent uptake without any particulate carrier.[18,19] These constructs are therefore administered subcutaneously, at intervals of three to six months. Inclisiran silences hepatic PCSK9 synthesis, increases LDL-receptor recycling, and lowered LDL-C by approximately 50% in the phase 3 ORION-10 and ORION-11 trials,[20] with confirmatory data in heterozygous

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**Table 2: Critical comparison of nanocarrier platforms by advantages, limitations, and clinical translation status.**

| Platform | Advantages | Key limitations | Clinical translation / applicability |
|---|---|---|---|
| Lipid-based (liposomes / LNPs) | Most mature manufacturing base; regulatory precedent from mRNA vaccines and patisiran; efficient nucleic-acid protection and hepatocyte delivery | Anti-PEG immunogenicity on repeat dosing; hepatic tropism limits use outside liver-directed indications; cold-chain requirements for some formulations | High for hepatic RNA and gene-editing delivery (patisiran approved; LNP-CRISPR in phase 1); plaque-targeted liposomes: no benefit in an early-phase trial |
| Ligand-conjugated siRNA (GalNAc-siRNA) | No particulate carrier required; subcutaneous dosing every 3-6 months; robust, durable gene silencing | Confined to hepatocyte targets (ASGPR); not applicable to plaque, myocardium, or thrombus delivery | Highest: inclisiran and vutrisiran approved; ORION-4 outcomes results expected early 2027 |
| Polymeric (PLGA/PLA, chitosan, dendrimers) | Precise, tunable release kinetics; well-characterised biodegradation; flexible surface chemistry for multivalent ligand display | Comparatively modest active-targeting efficiency in systemic use; organic-solvent residues; scale-up variability | High for local/device-based delivery (drug-eluting stents, more than two decades of use); low for systemic injectable use, which remains preclinical |
| Polymeric micelles | Simple, reproducible self-assembly; effective solubilisation of poorly water-soluble agents; relatively low manufacturing cost | Thermodynamic instability below the critical micelle concentration can cause premature drug release in the circulation | Low: no late-stage cardiovascular evidence identified; value mainly as a solubilisation strategy |
| Inorganic (gold, SPION, mesoporous silica) | Intrinsic imaging contrast enabling theranostic design; stable, reproducible physicochemical properties; stimuli-triggerable (photothermal/magnetic) | Non-biodegradable cores raise chronic biopersistence and long-term toxicity concerns; narrower therapeutic index than organic carriers | Low-to-moderate: iron oxide agents used for imaging; therapeutic (non-imaging) use remains preclinical |
| Biomimetic / cell-membrane-coated | Prolonged circulation half-life; natural immune evasion; innate affinity for injured endothelium, plaque, or thrombus | Donor-membrane isolation causes batch-to-batch variability; not yet compatible with scalable GMP production; allogeneic sourcing raises immunological questions | Earliest stage: mechanistically the most sophisticated platform but confined to preclinical proof-of-concept studies |
| Extracellular vesicles (emerging) | Natural targeting and low immunogenicity; endogenous cargo transfer; no synthetic core | Heterogeneous populations; low yield; non-standardised isolation and potency assays; limited GMP experience | Preclinical for therapy; registered trials mainly evaluate EVs as biomarkers |

Abbreviations: ASGPR, asialoglycoprotein receptor; GMP, Good Manufacturing Practice; LNP, lipid nanoparticle; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); SPION, superparamagnetic iron oxide nanoparticle; EVs, extracellular vesicles.

familial hypercholesterolaemia (ORION-9).[21] Vutrisiran, also GalNAc-conjugated, silences hepatic TTR production.[22]

These conjugates are included here because they define the clinical benchmark against which particulate cardiovascular carriers must be judged. Their success reflects the exceptional tractability of hepatocyte targeting rather than the maturity of nanoparticle engineering in general.

## Polymeric nanoparticles

Biodegradable polymers such as Poly (Lactic-Co-Glycolic Acid) (PLGA), Polylactic Acid (PLA), chitosan, and polyamidoamine dendrimers offer sustained and controllable drug release through hydrolytic or enzymatic degradation of the polymer matrix.[23,24] The principal advantage of polymeric systems is precise, tunable control over release kinetics through polymer molecular weight and copolymer ratio.

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**Table 3: Approved and late-stage nucleic-acid and nanotechnology-based cardiovascular therapeutics and key clinical evidence.**

| Agent | Platform and route | Target / indication | Key clinical evidence | Status |
|---|---|---|---|---|
| Inclisiran | GalNAc-siRNA conjugate (non-LNP); subcutaneous, twice-yearly maintenance | Hepatic PCSK9; hypercholestero-laemia | ORION-10/11: LDL-C reduced by approximately 50%[20]; ORION-9 in heterozygous familial hypercholesterolaemia[21]; ORION-4 (about 15,000 participants) ongoing[37] | Approved for LDL-C lowering; outcomes results expected early 2027 |
| Vutrisiran | GalNAc-siRNA conjugate (non-LNP); subcutaneous, every 3 months | Hepatic TTR; ATTR-CM | HELIOS-B ($n$ = 655): composite of all-cause mortality and recurrent cardiovascular events, hazard ratio 0.72[22] | Approved for ATTR-CM and hereditary ATTR polyneuropathy |
| Patisiran | LNP-formulated siRNA; intravenous, every 3 weeks | Hepatic TTR; hereditary ATTR polyneuropathy; ATTR-CM | APOLLO in polyneuropathy[14]; APOLLO-B ($n$ = 359): improved 6-minute walk distance at 12 months[40] | Approved for hereditary ATTR polyneuropathy; ATTR-CM evaluated in phase 3 |
| CTX310 | LNP-encapsulated CRISPR-Cas9 mRNA and guide RNA; single intravenous dose | Hepatic ANGPTL3; refractory dyslipidaemia | Phase 1 (15 participants with at least 60 days of follow-up): dose-dependent reductions in ANGPTL3, triglycerides, and LDL-C; no dose-limiting toxicity[17] | Investigational (phase 1) |
| Zilebesiran | GalNAc-siRNA; subcutaneous | Hepatic angiotensinogen; hypertension | Early-phase trial data[38] | Investigational |
| Olpasiran | GalNAc-siRNA; subcutaneous | Hepatic lipoprotein(a); atherosclerotic cardiovascular disease | Phase 2 dose-finding data[39] | Investigational (phase 3 development) |
| Liposomal prednisolone | PEGylated liposome; intravenous | Plaque macrophages; vascular inflammation | Delivered to plaque macrophages, but no reduction in arterial inflammation in a 30-patient randomised study[12] | No efficacy signal in early-phase trial |
| Sirolimus / paclitaxel-eluting stents and balloons | Polymer-coated device; local delivery | Restenosis after percutaneous coronary intervention | Randomised evidence of reduced restenosis[25] | In widespread clinical use (device-based) |

Abbreviations: ANGPTL3, angiopoietin-like protein 3; ATTR-CM, transthyretin amyloid cardiomyopathy; GalNAc, N-acetylgalactosamine; LDL-C, low-density lipoprotein cholesterol; LNP, lipid nanoparticle; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering ribonucleic acid; TTR, transthyretin. Status reflects information available at the time of the September 2026 update and should be confirmed against current regulatory labelling.

Polymeric coatings underpin Drug-Eluting Stents (DES) and Drug-Coated Balloons (DCB) that suppress neointimal hyperplasia and restenosis after percutaneous coronary intervention.[25] Strictly, these are device-based polymer systems rather than injectable nanoparticles, but they represent the most extensively validated polymeric drug-delivery technology in cardiovascular medicine. Dendrimeric carriers, with their precisely defined branching architecture, permit high-density conjugation of targeting ligands or multiple drug molecules and have been investigated for combined anti-inflammatory and antithrombotic plaque therapy, but remain preclinical.

By contrast, systemic (non-device) polymeric nanoparticle therapy for direct anti-atherosclerotic or cardioprotective indications has not progressed beyond preclinical proof of concept. Contributing factors include comparatively modest active-targeting efficiency relative to biomimetic or ligand-functionalised lipid carriers, together with residual-solvent and batch-reproducibility concerns during scale-up.[5,23]

## Polymeric micelles

Amphiphilic block-copolymer micelles, typically self-assembled from Polyethylene Glycol-Polylactic Acid (PEG-PLA) or related copolymers, form a hydrophobic core capable of solubilising

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**Table 4: Emerging technologies in cardiovascular nanomedicine: current evidence, barriers, and priority needs.**

| Direction | Current evidence | Principal barriers | Priority needs |
|---|---|---|---|
| AI-assisted nanoparticle design | Computational screening of ionisable-lipid libraries and AI-guided LNP design.[43,44] | Small, heterogeneous datasets; training largely on hepatic or rodent data; limited external validation. | Open, standardised cardiovascular biodistribution datasets; prospective validation in large animals. |
| Extracellular vesicles | Preclinical cardiac and vascular delivery; clinical trials mainly biomarker studies.[46,47] | Heterogeneity, low yield, non-standardised isolation and potency assays, limited GMP experience. | GMP-compatible isolation; potency assays; adherence to minimal-information reporting.[48] |
| LNP gene editing | Primate PCSK9 base editing;[16] phase 1 ANGPTL3 editing.[17] | Irreversibility; off-target editing; small trials with short follow-up; cost | Long-term safety registries; initial use in refractory or genetic dyslipidaemia |
| Precision nanomedicine | Conceptual; supported by stratified RNAi therapy in ATTR-CM.[22] | Absence of companion diagnostics; regulatory frameworks for combination products | Biomarker-stratified trial designs; companion diagnostics; adaptive regulatory pathways |

Abbreviations: AI, artificial intelligence; ANGPTL3, angiopoietin-like protein 3; GMP, Good Manufacturing Practice; LNP, lipid nanoparticle; PCSK9, proprotein convertase subtilisin/kexin type 9; RNAi, ribonucleic acid interference; ATTR-CM, transthyretin amyloid cardiomyopathy.

poorly water-soluble cardiovascular agents such as statins, surrounded by a hydrophilic PEG corona that confers colloidal stability and prolongs circulation.[25] Their principal value lies in improving the bioavailability of established small molecules rather than enabling fundamentally new mechanisms of action. Their main limitation is thermodynamic instability below the critical micelle concentration, which can precipitate premature drug release following intravenous dilution. We identified no micellar formulation with late-stage cardiovascular clinical evidence.

## Inorganic nanoparticles

Gold nanoparticles, Superparamagnetic Iron Oxide Nanoparticles (SPIONs), and mesoporous silica nanoparticles combine drug-carrying capacity with intrinsic imaging contrast, supporting theranostic applications in which diagnosis and therapy are integrated within a single platform.[26] SPIONs enable Magnetic Resonance Imaging (MRI)-based visualisation of atherosclerotic plaque composition and macrophage infiltration, while also permitting magnetically guided localisation of the carrier at the target site. Gold nanoparticles additionally support photothermal ablation of plaque macrophages upon near-infrared irradiation, offering a light-triggered therapeutic modality alongside conventional drug release.

Their principal limitation is a narrower therapeutic index than organic carriers: non-biodegradable metallic or silica cores raise long-term biopersistence and chronic toxicity concerns that have so far restricted clinical use of inorganic nanocarriers largely to imaging contrast rather than sustained cardiovascular drug delivery.[5,26]

## Biomimetic and cell-membrane-coated nanoparticles

A more recent innovation involves cloaking synthetic nanoparticle cores with membranes derived from platelets, macrophages, or Red Blood Cells (RBCs), conferring the natural surface antigen profile and adhesion machinery of the source cell.[27] Platelet-membrane-coated nanoparticles retain the glycoprotein receptors that mediate platelet adhesion to injured endothelium and exposed subendothelial collagen. In a landmark study, such particles showed reduced complement activation and macrophage uptake and adhered selectively to injured vasculature in a rat model of coronary restenosis.[28] Leukocyte-derived membrane coatings carrying rapamycin have likewise reversed vascular inflammation in a mouse model of atherosclerosis.[29]

Biomimetic coating confers arguably the most favourable circulation and immune-evasion profile among the platforms discussed here. However, donor-cell-membrane isolation, fusion, and purification introduce substantial batch-to-batch variability that currently limits scalable Good Manufacturing Practice (GMP) production, placing these carriers at an earlier stage of clinical readiness than lipid-based systems despite their mechanistic sophistication.[27]

## Cross-platform critical comparison

Three trade-offs recur across the platforms above. First, targeting sophistication is inversely related to manufacturability: biomimetic and ligand-decorated carriers offer the best circulation and homing profiles but the least reproducible production, whereas LNPs and polymers are scalable but rely largely on passive accumulation or hepatic tropism.[5] Second, payload dictates platform: nucleic acids currently favor LNPs or GalNAc conjugates, sustained small-molecule release favors polymers,

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and imaging-integrated therapy favors inorganic cores. Third, target organ dictates feasibility: delivery to hepatocytes is at present uniquely efficient, whereas delivery to plaque, infarcted myocardium, or thrombus, where most preclinical studies are conducted, remains unproven in humans.

Table 2 sets out these comparisons in detail, and Figure 3 (see Clinical translation) maps the resulting differences in translational maturity.

## Nanoparticle Applications Across Major Cardiovascular Indications

Figure 2 summarises how the targeting strategies of the platforms described above map onto the major cardiovascular indications discussed in this section.

## Atherosclerosis and plaque-targeted therapy

Atherosclerosis is characterized by lipid accumulation within the arterial intima, monocyte recruitment and differentiation into lipid-laden macrophages, and progressive fibrous plaque formation, with plaque rupture precipitating myocardial or cerebral infarction.[30] Nanoparticle strategies have concentrated on macrophage-targeted delivery of anti-inflammatory agents (for example, statins, corticosteroids, or liver-X-receptor agonists) using ligands directed against scavenger or mannose receptors overexpressed on plaque macrophages, thereby limiting foam-cell formation and necrotic core expansion.[31] Self-assembling nanoparticles incorporating native or modified lipoproteins, such as reconstituted High-Density Lipoprotein (HDL) nanoparticles, promote cholesterol efflux directly from plaque macrophages and combine a therapeutic and diagnostic function within a single biomimetic carrier.[32]

Original preclinical studies illustrate the range of approaches. A statin-loaded reconstituted HDL nanoparticle reduced plaque inflammation in mice;[33] siRNA nanoparticles silencing CaMKIIγ in lesional macrophages improved plaque stability;[34] and rapamycin-loaded biomimetic nanoparticles reversed vascular inflammation.[29] These results are encouraging but derive from mouse models with accelerated plaque development, and the only human test of a plaque-macrophage-targeted nanomedicine to date was negative (see Clinical translation).[12]

## Myocardial infarction and ischaemia-reperfusion injury

Following acute myocardial infarction, an intense inflammatory response involving neutrophil and monocyte infiltration contributes both to necrotic tissue clearance and to secondary myocardial injury during reperfusion.[35] Nanoparticle-encapsulated anti-inflammatory peptides, antioxidants, and small-molecule inhibitors of pro-inflammatory signalling have been designed to accumulate within the infarcted and peri-infarct myocardium via the locally disrupted vasculature, limiting infarct expansion and adverse ventricular remodelling.[36] Nanocarriers loaded with pro-angiogenic growth factors or cardioprotective microRNAs are additionally under investigation to promote neovascularisation and attenuate fibrotic scar formation, though most such approaches remain preclinical.

Key unresolved issues are the narrow therapeutic window around reperfusion, the limited access of circulating carriers to the ischaemic zone after vessel occlusion, and the scarcity of large-animal efficacy data.

## Dyslipidaemia and RNA-based lipid lowering

Hepatocyte-directed RNA delivery has enabled the most clinically advanced application of cardiovascular nanomedicine to date. GalNAc-conjugated siRNA against PCSK9 (inclisiran) has converted PCSK9 silencing from a laboratory concept into a licensed therapy administered as infrequently as twice yearly, with durable LDL-C reduction and a favourable tolerability profile across the ORION programmed.[20,21] Ongoing outcome trials, most notably ORION-4, are evaluating whether this effect translates into fewer major adverse cardiovascular events.[37]

Genuinely particulate delivery is now entering the same space through LNP-based gene editing. A base editor delivered by LNP durably lowered PCSK9 and LDL-C in primates.[16] In a phase 1 trial including 15 participants with at least 60 days of follow-up, a single intravenous dose of CTX310, an LNP-encapsulated CRISPR-Cas9 mRNA and guide RNA targeting hepatic ANGPTL3, produced dose-dependent reductions in atherogenic lipids without dose-limiting toxic effects.[17] The irreversibility of editing makes long-term safety surveillance essential.

The same GalNAc-siRNA approach is being applied to other cardiovascular targets, including angiotensinogen for hypertension (zilebesiran, early-phase trials).[38] and lipoprotein(a) (olpasiran, phase 2, now in phase 3 development).[39]

## Thrombosis and stimuli-responsive thrombolytic delivery

In thromboembolic disease, nanoparticles functionalised with fibrin- or activated-platelet-binding ligands have been developed to concentrate thrombolytic agents such as tissue plasminogen activator at the site of clot formation, reducing the systemic bleeding risk associated with conventional intravenous thrombolysis.[27] Stimuli-responsive designs that release their payload in response to the elevated shear stress at a stenotic or occluded vessel segment represent a further refinement, restricting thrombolytic activity to the pathological site. All such systems remain at the preclinical stage.

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### Restenosis prevention and local vascular delivery

Polymeric coatings incorporated into drug-eluting stents and drug-coated balloons provide sustained local release of anti-proliferative agents such as sirolimus and paclitaxel, suppressing smooth-muscle-cell proliferation and neointimal hyperplasia after percutaneous coronary intervention while limiting systemic exposure relative to oral administration.[25]

## CLINICAL TRANSLATION AND REGULATORY STATUS

Because clinical translation is central to the title and purpose of this review, this section considers in turn the approved RNA-interference (RNAi) therapeutics, later-stage and first-in-human programmes, device-based polymeric technologies, early clinical experience with plaque-targeted particulate carriers, and the regulatory landscape, before summarising the barriers that separate these categories. Table 3 consolidates the principal agents, and Figure 3 maps the translational maturity of each platform.

### Approved RNA-interference therapeutics

Inclisiran, a GalNAc-conjugated siRNA (see above), is the most clinically advanced nucleic-acid cardiovascular therapeutic. It is approved by major regulatory authorities as an LDL-C-lowering therapy on the basis of the ORION phase 3 programmed, which showed durable reductions in LDL-C of approximately 50% with twice-yearly maintenance dosing, and injection-site reactions as the principal excess adverse event.[20,21] Because ORION-9, ORION-10, and ORION-11 used LDL-C as the primary endpoint, a cardiovascular-risk-reduction claim awaits outcomes data.

ORION-4, a double-blind placebo-controlled trial of approximately 15,000 participants with established atherosclerotic cardiovascular disease, is expected to complete follow-up in 2026 with results anticipated in early 2027.[37] Its findings will determine whether inclisiran is positioned as an adjunct to statin therapy or as a foundational lipid-lowering agent, and will provide the first large-scale safety assessment of prolonged siRNA exposure.[37]

Vutrisiran, a GalNAc-conjugated siRNA administered subcutaneously every three months, was first approved for the polyneuropathy of hereditary transthyretin-mediated amyloidosis and has since been approved for transthyretin amyloid cardiomyopathy (ATTR-CM). In the HELIOS-B trial, 655 patients with ATTR-CM, a progressive infiltrative cardiomyopathy that overlaps substantially with the heart-failure population, were randomised to vutrisiran or placebo. Over a 36-month double-blind period, vutrisiran reduced the composite of all-cause mortality and recurrent cardiovascular events by approximately 28% (hazard ratio 0.72), with benefit sustained through 42 months of follow-up and a safety profile consistent with earlier studies.[22]

HELIOS-B is a milestone for RNAi therapy rather than for particulate nanomedicine, because vutrisiran is a GalNAc conjugate and not an LNP. The corresponding LNP-formulated agent, patisiran, improved functional capacity (6-minute walk distance) in ATTR-CM in the 359-patient APOLLO-B trial, a 12-month study powered for functional capacity rather than clinical events,[40] building on the APOLLO trial in hereditary ATTR polyneuropathy.[14] Although ATTR-CM is distinct from atherosclerotic disease, these trials show that RNA silencing can favorably alter hard cardiovascular outcomes. They also show that the translational pathway of cardiovascular nucleic-acid nanomedicine has been narrower than the preclinical literature suggests, running almost exclusively through hepatocyte-directed gene silencing rather than through the plaque- or myocardium-targeted carriers that dominate preclinical work.

### Later-stage and first-in-human programmes

LNP-based gene editing has reached first-in-human testing: the CTX310 study provided initial evidence that a single infusion can lower ANGPTL3 and atherogenic lipids without dose-limiting toxicity, although the study was small and follow-up short.[17] GalNAc-siRNA agents against angiotensinogen and lipoprotein(a) have progressed through early-phase trials.[38,39] Across nanomedicine generally, marketed products remain dominated by liposomes and LNPs.[41]

### Device-based polymeric drug delivery

Drug-eluting stents represent an intermediate translational example in which polymeric drug-carrier technology, rather than a discrete injectable nanoparticle, has achieved widespread clinical use for more than two decades.[25] They remain the most extensively validated nanoparticle-adjacent drug-delivery technology in cardiovascular medicine in terms of cumulative patient exposure.

### Early clinical experience with plaque-targeted particulate carriers

Clinical experience with injectable, plaque-targeted particulate carriers is very limited and instructive. In the first clinical studies of a PEGylated liposomal prednisolone, intravenous infusion delivered liposomes to plaque macrophages (they were detected in 75% of macrophages isolated from plaques of patients undergoing vascular surgery), yet in a subsequent randomised, placebo-controlled study of 30 patients the formulation did not reduce arterial wall permeability or inflammation on multimodal imaging.[12] This result shows that successful delivery is necessary but not sufficient: target-site accumulation must be coupled to a pharmacological mechanism that is validated in humans.

On the basis of the search described in the Methodology, we identified no plaque-targeted liposomal, polymeric, inorganic, or biomimetic nanoparticle in registered phase 3 evaluation

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for a primary cardiovascular indication, and published human experience with these platforms is limited to small early-phase pharmacokinetic and imaging-based studies rather than outcome-driven trials.[11] This gap between an extensive preclinical evidence base and a very narrow clinical pipeline is, in our view, the single most important translational challenge facing cardiovascular nanomedicine outside the RNA-therapeutic domain, and is examined further in the following section.

### Regulatory considerations

Regulatory frameworks for nanomedicines are evolving. The US FDA guidance on drug products containing nanomaterials addresses quality, non-clinical, and clinical considerations.[3] In India, the Department of Biotechnology, the Indian Council of Medical Research, and the Central Drugs Standard Control Organization jointly released guidelines for the evaluation of nanopharmaceuticals in 2019, which supplement the general requirements for new drugs and clinical trials.[42] Recurring regulatory challenges include defining critical quality attributes for multi-component carriers, demonstrating comparability after manufacturing scale-up, and assessing long-term biopersistence and immunogenicity.[3,5] Theranostic combination products and cell-derived products such as EVs raise further classification questions that current frameworks do not fully resolve.

## CHALLENGES AND LIMITATIONS

Despite considerable preclinical promise, several challenges continue to limit the clinical adoption of cardiovascular nanomedicine:

### Scale-up and batch-to-batch reproducibility

Transition from laboratory-scale synthesis to GMP production while maintaining consistent particle size, drug loading, and surface functionalisation remains technically demanding, and is most acute for biomimetic carriers and EVs.

### Long-term biocompatibility and immunogenicity

Repeated administration of PEGylated or biomimetic carriers may provoke anti-PEG antibody responses or complement activation, potentially accelerating clearance or triggering hypersensitivity reactions.[5]

### Off-target accumulation

Hepatic and splenic uptake by the mononuclear phagocyte system diverts a substantial fraction of administered nanoparticles away from the intended cardiovascular target.[8] This tropism explains why hepatocyte-directed therapies have succeeded first.

### Uncertain passive targeting and model translatability

EPR-like accumulation is heterogeneous, and most efficacy data derive from mouse models with rapid plaque development that poorly reflect chronic human disease; large-animal and imaging-based human studies are scarce.[8]

### Protein-corona formation

Plasma proteins adsorbed onto the particle surface alter its biological identity and can neutralize engineered targeting ligands *in vivo*.[5]

### Cost, access, and regulatory complexity

The multi-component nature of nanoparticle formulations (core, surface ligand, targeting moiety) increases characterisation requirements and cost relative to conventional small-molecule products; cost and access are especially pertinent where cardiovascular disease burden is high and health-system resources are constrained.

### Limited long-term human safety data

Chronic cardiovascular conditions require sustained or repeated dosing, and long-term safety data for many novel carriers, and for irreversible gene-editing approaches, remain sparse relative to decades of experience with conventional formulations.

Addressing these limitations will require closer integration of formulation science, regulatory science, and large-scale manufacturing expertise as candidate nanomedicines progress from preclinical proof of concept towards clinical evaluation.[11]

## FUTURE DIRECTIONS

Future development is likely to focus on multifunctional theranostic nanoparticles that combine diagnostic imaging with therapeutic delivery, stimuli-responsive systems that release payload selectively in response to disease-specific biochemical or mechanical cues, and further refinement of biomimetic coating strategies to improve targeting specificity while minimising immunogenicity.[36] The convergence of nanoparticle engineering with RNA-based therapeutics is expected to extend beyond PCSK9 and transthyretin silencing to additional cardiovascular gene targets, capitalising on the regulatory and manufacturing precedent already established by inclisiran, vutrisiran, and patisiran. Four areas merit detailed evaluation, and Table 4 and Figure 4 summarize their status and prerequisites.

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## Artificial-intelligence-assisted nanoparticle design

Machine-learning and deep-learning methods are increasingly applied across the nanomedicine development pipeline, from target identification through formulation optimisation to toxicity prediction and personalized dosing.[43] Supervised learning, graph neural networks, and generative models have been used to predict nanoparticle behavior and to screen ionisable-lipid libraries computationally, with transformer-based architectures reported to identify effective lipid candidates from libraries of several thousand trial formulations.[43]

Applied specifically to LNPs, AI-guided approaches model the relationships between composition, physicochemical properties, and *in vivo* delivery efficiency, with the explicit goal of shortening the iterative design-test cycle that currently constrains the development of new siRNA- and mRNA-LNP candidates.[44] For cardiovascular nanomedicine, such tools could in principle be directed towards optimising ligand density and particle geometry for plaque- or myocardium-targeted carriers, the translational gap identified above.

Three limitations temper this optimism. First, most published models are trained on *in vitro* or rodent hepatic-delivery data and may not generalise to plaque, myocardium, or human physiology. Second, datasets are small, heterogeneous, and rarely shared, so external validation and benchmarks are scarce. Third, AI shortens the design-test cycle but does not remove the need for large-animal and clinical validation, and clear regulatory expectations for AI-derived formulation decisions are still developing. Standardised, openly reported cardiovascular-specific datasets, including biodistribution to plaque and myocardium, are the enabling prerequisite; at present this application remains largely aspirational.

## LNP-enabled *in vivo* gene editing

Beyond siRNA, LNPs are enabling one-time *in vivo* genome editing of hepatic lipid-regulatory genes, with preclinical PCSK9 base editing in primates and first-in-human ANGPTL3 editing already reported.[16,17] The attraction is a durable, potentially single-dose therapy for chronic lipid disorders. The open questions are long-term safety, off-target editing, ethical acceptability of irreversible modification in common cardiometabolic disease, and cost. A pragmatic route is initial evaluation in patients with refractory or genetic dyslipidaemia, where the benefit-risk balance is most favourable.

## Extracellular vesicles as a natural extension of biomimetic delivery

Extracellular Vesicles (EVs), including exosomes and microvesicles, are endogenous, cell-derived nanoscale carriers that share several advantages of biomimetic cell-membrane-coated nanoparticles, namely natural surface antigen expression, low intrinsic immunogenicity, and an innate capacity for intercellular cargo transfer, while avoiding the synthetic-core fabrication step that biomimetic nanoparticles require.[45] In cardiovascular disease, EVs have been explored both as biomarkers of disease activity and, increasingly, as engineered carriers for anti-inflammatory, antithrombotic, and pro-angiogenic cargo directed at myocardial infarction, atherosclerosis, and heart failure.[46,47] Platelet-derived EVs in particular retain the endothelial- and collagen-binding machinery of their parent cells, offering a route to injured-vasculature targeting that parallels platelet-membrane-coated synthetic nanoparticles.

Engineering strategies include loading therapeutic cargo into EVs and displaying targeting ligands on their surface.[45] Nevertheless, EV-based therapeutics for cardiac repair remain almost entirely preclinical, with registered clinical trials predominantly evaluating EVs as diagnostic biomarkers rather than therapeutic agents.[46,47] Heterogeneity in EV populations, low yields, co-isolation of non-vesicular contaminants, and the lack of standardised potency assays are prerequisites to be resolved, and consistent reporting in line with current minimal-information guidelines is required for comparability between studies.[48]

## Towards precision cardiovascular nanomedicine

Taken together, AI-assisted formulation design, EV engineering, LNP gene editing, and continued refinement of stimuli-responsive and biomimetic coatings point towards a longer-term goal of precision cardiovascular nanomedicine, in which carrier composition, targeting ligand, and release trigger are matched to an individual patient's plaque phenotype, inflammatory profile, or genetic risk factors rather than applied uniformly across a diagnostic category.[17,20,22,40]

Realising this goal will require not only further engineering advances but also companion diagnostic development, prospective biomarker-stratified trial designs, and regulatory frameworks capable of evaluating combination diagnostic-therapeutic products.[12] Continued collaboration between pharmaceutical scientists, cardiologists, data scientists, and regulatory bodies will be essential to translate these innovations into approved therapies that meaningfully improve cardiovascular outcomes.

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## CONCLUSION

The evidence reviewed here supports three critical conclusions. First, cardiovascular nanomedicine has achieved regulatory approval and demonstrable patient benefit through a single, narrow translational pathway, hepatocyte-directed RNA silencing, exemplified by GalNAc-conjugated inclisiran for PCSK9-mediated lipid lowering and, more recently, by vutrisiran's reduction in mortality and cardiovascular events in ATTR cardiomyopathy, with LNP-formulated patisiran and first-in-human LNP gene editing extending the same logic to particulate carriers. This success validates RNA-based delivery but should not be over-generalised: it reflects the particular tractability of hepatocyte targeting rather than proof that plaque-, thrombus-, or myocardium-targeted nanomedicine is equally close to the clinic.

Second, the much larger literature on liposomal, polymeric, inorganic, and biomimetic carriers for direct anti-atherosclerotic, cardioprotective, and thrombolytic therapy remains preclinical, and its one clinical test, liposomal prednisolone, delivered the drug to plaque macrophages without an anti-inflammatory effect. The field's near-term priority should therefore be to close the gap between mechanistic sophistication and clinical validation, rather than to continue to expand the number of preclinical platforms described. Third, emerging directions, including AI-assisted formulation design, EV-based carriers, LNP gene editing, and biomarker-stratified precision nanomedicine, offer plausible routes to accelerate translation, but each introduces manufacturing, standardisation, safety, or regulatory prerequisites that are not yet resolved.

We propose the following research priorities:

**Standardised comparison:** head-to-head, large-animal efficacy and biodistribution studies using harmonised protocols, so that platforms can be compared on equal terms.

**Human target-engagement first:** early-phase imaging studies that confirm accumulation at plaque, myocardium, or thrombus before efficacy trials are launched.

**Mechanism-first candidate selection:** pairing carriers with payloads whose pharmacology is already validated in humans, to avoid repeating the liposomal prednisolone outcome.

**Early manufacturing and regulatory science:** defining critical quality attributes and scalable GMP processes for biomimetic carriers and EVs at the preclinical stage.

**Shared data and long-term safety:** open cardiovascular-specific formulation datasets for AI models, biomarker-stratified trial designs, and long-term registries for gene-editing therapies.

Continued attention to these priorities, building on the template established by the inclisiran, vutrisiran, and patisiran programmes, will determine the pace at which the wider promise of cardiovascular nanomedicine is realized in routine clinical practice.

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## ABBREVIATIONS

**AI:** Artificial Intelligence; **ALN-PCS:** Early Intravenous PCSK9-Targeted siRNA-Lipid Nanoparticle Candidate; **ANGPTL3:** Angiopoietin-Like Protein 3; **ASGPR:** Asialoglycoprotein Receptor; **ATTR-CM:** Transthyretin Amyloid Cardiomyopathy; **CDSCO:** Central Drugs Standard Control Organization; **CVDs:** Cardiovascular Diseases; **DBT:** Department of Biotechnology; **DCB:** Drug-Coated Balloon; **DES:** Drug-Eluting Stent; **EPR:** Enhanced Permeability and Retention; **EVs:** Extracellular Vesicles; **GalNAc:** N-Acetylgalactosamine; **GMP:** Good Manufacturing Practice; **HDL:** High-Density Lipoprotein; **ICMR:** Indian Council of Medical Research; **LDL-C:** Low-Density Lipoprotein Cholesterol; **LNPs:** Lipid Nanoparticles; **mRNA:** Messenger Ribonucleic Acid; **MRI:** Magnetic Resonance Imaging; **NPs:** Nanoparticles; **PCSK9:** Proprotein Convertase Subtilisin/Kexin Type 9; **PEG-PLA:** Polyethylene Glycol-Polylactic Acid; **PLA:** Polylactic Acid; **PLGA:** Poly(lactic-co-glycolic acid); **RBC:** Red Blood Cell (Erythrocyte); **RNAi:** Ribonucleic Acid Interference; **ROS:** Reactive Oxygen Species; **siRNA:** Small Interfering Ribonucleic Acid; **SPION(s):** Superparamagnetic Iron Oxide Nanoparticle(s); **TTR:** Transthyretin.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

**Goday Swapna:** Conceptualisation of the review, literature search and screening, drafting of the original manuscript, and critical revision and approval of the final version submitted for publication.

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