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DOI: <https://doi.org/10.21542/gcsp.2026.46>
VOLUME: 2026
ISSUE: 5
ARTICLE: 46

PMC PUBLICATION DATE: 31 Oct 2026
PMC COLLECTION DATE: 31 Oct 2026
PMC ARTICLE TYPE: review-article

ARTICLE TYPE: Review article
SUBMITTED: 18 Aug 2026
ACCEPTED: 13 Oct 2026
RUNNING HEAD: Nag et al., GCSP 2026:46

CITE THIS ARTICLE AS: Nag R, Raza ST, Almahmeed WA, Mahdi F. Extracellular vesicles in cardiovascular diseases: From molecular signatures to therapeutic applications, Global Cardiology Science and Practice 2026:46 <https://doi.org/10.21542/gcsp.2026.46>

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Extracellular vesicles in cardiovascular diseases: From molecular signatures to therapeutic applications

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Abstract

Cardiovascular diseases (CVDs) remain the leading cause of global morbidity and mortality, emphasizing the need for sensitive biomarkers and effective therapeutic strategies. Extracellular vesicles (EVs) are membrane-bound nanoparticles released by virtually all cell types that mediate intercellular communication through the transfer of proteins, lipids, messenger RNAs, microRNAs and DNA. Increasing evidence indicates that alterations in EV cargo contribute to the initiation and progression of multiple cardiovascular disorders, while also offering opportunities for minimally invasive diagnosis and targeted therapy.

This review summarizes current evidence on the molecular mechanisms, diagnostic significance and therapeutic applications of EVs across major cardiovascular diseases, including atherosclerosis, coronary artery disease, myocardial infarction, heart failure, atrial fibrillation, valvular heart disease and cardiomyopathies. Disease-specific EV-associated proteins and non-coding RNAs, particularly microRNAs, are discussed as candidate biomarkers for diagnosis, risk stratification, prognosis and treatment monitoring. The review also highlights emerging EV-based therapeutic approaches, including regenerative medicine, engineered EVs and targeted drug delivery systems, while critically discussing translational challenges such as EV heterogeneity, lack of standardized isolation and characterization protocols, scalability, regulatory considerations and the need for robust clinical validation. Most mechanistic and therapeutic evidence remains preclinical and EV biomarker assays are not yet established for routine care. In conclusion, EVs represent a promising platform for advancing precision cardiovascular medicine by integrating molecular diagnostics with innovative therapeutic strategies. Although substantial progress has been achieved, overcoming current technical, regulatory and clinical challenges through standardized methodologies and large-scale validation studies is essential for translating EV-based technologies into routine cardiovascular practice.

Introduction

Cardiovascular diseases remain the leading cause of mortality worldwide. The Global Burden of Cardiovascular Diseases and Risks 2023 Collaborators estimated 19.2 million cardiovascular deaths and 626 million prevalent cases globally in 2023, underscoring the continuing need for effective preventive and therapeutic strategies.¹

EVs are small membrane-bound particles enclosed by a lipid bilayer. In addition to direct physical interaction and paracrine signaling, EVs are recognized as mediators of cell-to-cell communication. They carry bioactive material, including proteins, lipids, mRNAs, microRNAs and DNA, between cells. EVs may modify gene expression, fine-tune cell signaling and affect cellular responses, with beneficial, neutral or adverse effects depending on their cellular origin and biological context.²⁻⁴

EV populations are heterogeneous. The terms “exosome” and “microvesicle” refer to endosomal and plasma-membrane biogenesis, respectively and should be used only when biogenesis has been demonstrated. Apoptotic bodies arise through membrane blebbing and cell disassembly during apoptosis. Reported size ranges overlap in biological samples; size alone cannot establish biogenesis or function. Apoptotic bodies may contain cell debris, DNA and proteins.^{3,5}

Studies have revealed that EVs are secreted by cardiovascular-related cells, including cardiomyocytes, endothelial cells, fibroblasts, platelets, smooth muscle cells and immune cells. During normal physiological states, EVs may contribute to the maintenance of cardiac structure and function. During disease, changes in EV cargo may influence disease processes. Based on this rationale, interest has increased in the potential diagnostic and therapeutic roles of EVs in cardiovascular diseases (Figure 1, Tables 1–3).²⁻⁴

Methodology

Literature search and data synthesis

This narrative review was conducted through a comprehensive literature search of PubMed/MEDLINE, Scopus and Web of Science to identify studies evaluating the role of EVs in cardiovascular diseases, including atherosclerosis, coronary artery disease, myocardial infarction, heart failure, cardiomyopathies, atrial fibrillation and valvular heart disease. The search included articles published up to January 2026 using combinations of Medical Subject Headings (MeSH) and free-text terms including "extracellular vesicles", "exosomes", "microvesicles", "apoptotic bodies", "microRNAs", "cardiovascular diseases" and disease-specific keywords.

Only peer-reviewed articles published in English were included. Experimental (in vitro and in vivo), translational and clinical studies evaluating the biological, diagnostic or therapeutic roles of EVs in cardiovascular diseases were considered, while studies focusing exclusively on non-cardiovascular conditions, conference abstracts and non-English publications were excluded. Reference lists of relevant articles were manually screened to identify additional eligible studies.

As this is a narrative review, a formal systematic review methodology and PRISMA framework were not applied. The searches identified 311 records in PubMed/MEDLINE, 486 in Scopus and 402 in Web of Science (1,199 records in total). After removal of 296 duplicates, 903 records were screened by title and abstract. Of these, 794 were excluded and 109 full-text articles were assessed. Eighty full-text articles were excluded because they did not meet the eligibility criteria, leaving 29 articles for the

narrative synthesis. A further 12 relevant articles were identified by screening reference lists, resulting in 41 included articles. Retrieved evidence was critically synthesised and organised according to major cardiovascular disease categories, with emphasis on molecular mechanisms, biomarker potential, therapeutic applications and translational relevance. Recent human biomarker studies, updated EV standards and the registered SECRET-HF study were added where relevant during revision; seminal earlier mechanistic studies were retained when they supplied the primary evidence for a specific finding.

Mechanistic basis of EV-mediated cardiovascular remodeling

EVs may contribute to cardiovascular remodeling by mediating intercellular communication between cardiomyocytes, endothelial cells, fibroblasts and immune cells. Under pathological conditions such as hypoxia, oxidative stress and inflammation, EV cargo may change and influence recipient-cell behavior through signaling pathways including NF- κ B, PTEN/AKT and STAT3.^{2,6} EV-associated microRNAs have been linked experimentally to endothelial dysfunction, fibrosis, apoptosis, macrophage polarization and angiogenesis. Apoptotic bodies released by endothelial cells and carrying miR-126 promote CXCL12-dependent vascular protection in experimental models.⁷ Cardiac fibroblast-derived EVs carrying miR-21-3p contribute to pathological hypertrophy and fibrotic remodeling.⁸ Similarly, diabetic cardiomyocyte-derived EVs impair endothelial function through transfer of miR-320 in experimental models.⁹

Importantly, EVs may exert both cardioprotective and maladaptive effects depending on their cellular origin and disease microenvironment. Stem cell-derived EVs have shown regenerative effects in experimental models by reducing cardiomyocyte apoptosis, modulating inflammation and enhancing angiogenesis following myocardial infarction.^{10,11} Conversely, EVs released from activated immune cells and stressed cardiomyocytes may amplify inflammatory signaling and adverse ventricular remodeling.^{12,13} Most mechanistic evidence remains preclinical and clinical validation studies remain limited.⁶

Given the diverse biological effects of EV-mediated signaling in cardiovascular remodeling, increasing attention has focused on their diagnostic and therapeutic potential across multiple cardiovascular diseases. The following sections summarize the disease-specific roles of EVs in cardiovascular pathology, emphasizing both biomarker applications and emerging therapeutic strategies.

Role of EVs in the diagnosis of cardiovascular disease

Increasing evidence indicates that EVs are being investigated as candidate non-invasive biomarkers for cardiovascular diseases, as they carry disease-specific molecular cargo that can be detected in circulating biofluids. EV-associated proteins, microRNAs (miRNAs) and lipids reflect the physiological and pathological state of their parent cells and may provide information for early diagnosis, risk stratification and prognosis.⁶

Compared with traditional tissue biopsies, EV-based liquid biopsy approaches are minimally invasive and allow repeated sampling, enabling longitudinal monitoring of disease progression and therapeutic response. Emerging evidence supports the diagnostic potential of EV profiling across multiple cardiovascular conditions, including atherosclerosis, myocardial infarction and valvular heart disease. Human evidence remains heterogeneous and clinical utility or incremental value over established biomarkers has not been consistently demonstrated.

Overall, EV-based profiling represents a promising complement to conventional imaging and circulating biomarkers. However, standardization of EV isolation, characterization and analytical methods remains essential to facilitate clinical translation and implementation in personalized cardiovascular diagnostics.⁶ Until independent validation is available, reported signatures should be considered research candidates rather than routine clinical assays.

Several EV isolation techniques, including ultracentrifugation, size-exclusion chromatography, immunoaffinity capture and polymer-based precipitation, enrich different particle populations and may co-isolate soluble proteins and lipoproteins. Collection tube, anticoagulant, processing delay, platelet activation, centrifugation, storage and freeze–thaw history can also alter measured EV profiles. These factors limit direct comparison of results across studies and reinforce the need for standardized methods. The listed approaches provide versatile options for EV research and clinical applications. Ongoing advances in microfluidic technologies and standardization efforts are expected to further improve isolation efficiency, reproducibility and the clinical translation of EV-based diagnostics and therapeutics.^{5,14]}

Human studies provide early quantitative evidence. In a training cohort of 98 participants and a separate validation cohort of 80, an aggregate serum EV profile incorporating particle concentration and CD62P/CD42a epitopes discriminated STEMI from controls (training AUC 0.969); the study reported non-inferiority to troponin in that cohort, but did not establish clinical benefit or broad external transportability.¹⁵ In the prospective LYCHEE cohort, 74 patients with HFmrEF were followed for a median of 6.5 months; leukocyte EV concentration was associated with systolic dysfunction progression (AUC 0.70, 95% CI 0.54–0.85; 13 progression events), but external validation and incremental value over NT-proBNP were not established.¹⁶

A 2025 study reported a three-miRNA plasma-EV panel for subclinical coronary atherosclerosis (miR-146b-5p, miR-4701-3p and miR-1180-3p; AUC 0.8281) using a small independent validation sample.¹⁷ In a post-ACS cohort of 4,541 participants, plasma extracellular miR-223-3p and miR-378c were associated with heart-failure hospitalization or cardiovascular death after adjustment for clinical factors and established biomarkers (fourth-quartile hazard ratios 0.61 [95% CI 0.43–0.85] and 1.39 [0.97–1.98], respectively). A separate 27-patient subset localized these miRNAs to EV and nonvesicular particle fractions; the larger-cohort associations therefore are plasma extracellular-RNA findings rather than EV-specific estimates.¹⁸

Taken together, EV markers have shown discrimination or prognostic associations in selected cohorts, but evidence of incremental value over high-sensitivity troponin or natriuretic peptides remains limited. The STEMI study reported non-inferiority to troponin, not definitive incremental clinical utility. The HFmrEF and post-ACS studies do not establish externally validated improvement over NT-proBNP or hs-cTn. EV assays remain investigational and require prospective comparison with established biomarkers.^{15,16,18}

Atherosclerosis and coronary artery disease (CAD)

EVs carrying associated miRNAs play a critical role in inflammatory responses as well as in coagulation cascades in endothelial cells, platelets, smooth muscle cells and immune cells, thereby perpetuating atherosclerosis and angiogenesis. In stable cases of CAD, circulating EVs may arise from multiple cellular sources. Serum EVs from patients with myocardial ischemia have been reported to regulate angiogenesis through a miR-939-mediated nitric oxide pathway in experimental assays.¹⁹

EVs released by activated endothelial cells and monocytes, especially those expressing adhesion molecules and coagulation factors, are potential early risk indicators for vascular disorders. Decreased levels of mitochondrial encoded MT-CO1 have been shown to be associated with a higher risk for future cardiovascular events in subjects with stable CAD.²⁰ EVs released by foam cells from macrophages contribute to disease progression by inducing mononuclear smooth muscle cell migration and adhesion by activating ERK and AKT (PKB) signaling pathways.¹²

Conversely, apoptotic bodies released by endothelial cells and enriched with miR-126 exert protective effects by facilitating endothelial repair and enhancing plaque stability. These EVs accelerate re-endothelialization following vascular injury and stimulate CXCL12 (formerly termed stromal cell-derived factor-1) production, thereby inhibiting endothelial apoptosis and promoting progenitor cell recruitment.⁷ Clinically, elevated EV-associated miR-126 and miR-199a levels correlate with a reduced incidence of major adverse cardiovascular events in patients with stable CAD.²¹

Endothelial microparticles carrying miR-222 reduced TNF- α -induced ICAM-1 expression in recipient endothelial cells in experimental systems.²² In diabetes-associated limb ischemia models, endothelial microparticles transferred miR-503 to pericytes and impaired pericyte function and endothelial-pericyte communication through targets including EFNB2 and VEGF.²³ These findings differ from microparticles isolated from human atherosclerotic plaques, which promoted endothelial ICAM-1-dependent monocyte adhesion and migration.²⁴

Shear stress-induced Kruppel-like factor 2 (KLF2) upregulates endothelial miR-143/145 signaling. EVs derived from KLF2-expressing endothelial cells communicate miR-143/145 to vascular smooth muscle cells and reduce atherosclerotic lesion formation in ApoE^{-/-} mice.²⁵

Although EV-associated miRNAs demonstrate both protective and pathogenic effects in atherosclerosis, their biological activity remains highly context dependent. Differences in cellular origin, inflammatory microenvironment and plaque stage may alter EV cargo composition and functional behavior.^{24,25}

Myocardial ischemia and myocardial infarction (MI)

In myocardial injury, MSC-derived EVs confer cardioprotection by delivering miR-182 to regulate macrophage polarization during ischemia-reperfusion injury,²⁶ while hypoxia-stimulated MSC-EVs promote cardiac repair through miR-125b-mediated inhibition of cardiomyocyte apoptosis following MI.¹⁰

Cardiovascular risk factors can alter circulating EV cargo and EV levels may increase during MI due to release from activated or apoptotic cells, supporting their investigation as biomarkers. Current evidence does not establish a validated EV-associated miRNA or inflammatory-protein signature for routine MI diagnosis. Human MI biomarker findings are summarized in the diagnostic section and Table 3.¹⁵

Experimental studies have reported the promising regenerative potential of EV-mediated cardioprotection, with growing evidence that optimizing donor cell source, hypoxic conditioning and isolation techniques can further enhance EV cargo composition and therapeutic efficacy.^{10,11,27}

Cardiac hypertrophy and heart failure

EVs may mediate bidirectional communication between cardiomyocytes and fibroblasts during cardiac hypertrophy and heart failure (HF). In a human study, EVs derived from patients with HF had

altered miR-21-5p and impaired regenerative potential in experimental assays; these were patient-derived HF EVs, not MSC-derived EVs and the findings do not establish a clinical prognostic assay.¹³

In contrast, fibroblast-derived EVs enriched with miR-21-3p induce cardiomyocyte hypertrophy by targeting sorbin and SH3 domain-containing protein 2 (SORBS2) and inhibition of miR-21-3p attenuates hypertrophy in angiotensin II-induced models.⁸

In experimental hypertrophy models, myocyte-derived HSP90 and IL-6 signaling through STAT3 contributed to collagen expression and fibrosis.²⁸ EVs derived from diabetic cardiomyocytes impair endothelial function via transfer of miR-320.⁹ In peripartum cardiomyopathy (PPCM), Halkein et al reported increased miR-146a and identified ERBB4, NRAS, NOTCH1 and IRAK1 among its targets. The study did not report this elevation in DCM or identify SUMO1 as the relevant target. PPCM has a dilated rather than hypertrophic phenotype.²⁹

Collectively, these findings suggest that EVs may contribute to maladaptive intercellular communication during heart failure progression.^{6,8,13}

Atrial enlargement and fibrillation

Atrial enlargement is closely linked to atrial fibrillation and pathological cardiac remodeling. In an engineered atrial tissue model, extracellular-matrix-derived EVs promoted cardiomyocyte growth and altered electrical activity.³⁰ This study did not establish circulating miR-21-3p or miR-199a-3p as markers of atrial enlargement or clinical atrial fibrillation; further human studies are needed.

Valvular heart disease (VHD)

EVs have been investigated as participants in cardiovascular calcification, including processes relevant to calcific aortic valve disease.³¹ Disease-specific EV cargo patterns in stressed human valves and their diagnostic value remain insufficiently characterized.

Current therapeutic protocols to mitigate the effects of VHD rely primarily on medication and/or surgery. Although MSC-derived EVs have shown effects in experimental cardiovascular studies, the cited literature does not establish efficacy for valvular inflammation, fibrosis or calcification. EV-based treatment for VHD remains a research direction rather than a validated therapeutic approach.^{31,32}

In calcific aortic valve disease, EVs have been studied in calcification and mineralization processes.³¹ The sources cited here do not establish engineered EVs carrying miR-302/367, miR-29 or let-7 as treatments for calcific valve disease, or demonstrate valve-targeted EV drug delivery. These approaches remain hypotheses for future primary studies rather than demonstrated therapies.

Cardiomyopathies (HCM and DCM)

Cardiomyopathies comprise a heterogeneous group of heart muscle disorders characterized by structural and functional abnormalities that may progress to heart failure. HCM is frequently associated with sarcomeric gene variants, including MYBPC3 and MYH7, whereas DCM has diverse genetic and acquired causes, including variants in TTN. These phenotypes have distinct clinical features but may share altered calcium handling, oxidative stress, mitochondrial dysfunction and myocardial remodeling.³³⁻³⁵

EVs are being investigated as potential mediators and biomarkers in cardiomyopathies. Under pathological stress, EV cargo may reflect cellular state and intercellular signaling. Reported candidate EV cargo includes miR-92b-5p in DCM-related acute heart failure and sEV-associated miR-15a-5p and miR-96-5p in HCM with myocardial fibrosis; these findings are not yet validated human biomarkers.

The miR-146a findings cited here apply to PPCM, not DCM.²⁹ Further well-characterized human studies are needed before EV profiling can support disease stratification or monitoring (Figure 2).

Extracellular vesicle–based therapeutic strategies across cardiovascular diseases

In atherosclerosis and CAD, EV-based therapeutic strategies aim to restore endothelial integrity, reduce inflammation and stabilize vulnerable plaques. Apoptotic bodies released by endothelial cells and enriched with miR-126 enhance endothelial repair by promoting re-endothelialization and stimulating stromal cell-derived factor-1 (SDF-1), thereby improving vascular healing and plaque stability.⁷ EVs derived from KLF2-expressing endothelial cells further suppress inflammatory signaling and reduce lesion formation in experimental models.²⁵ Therapeutically engineered EVs remain experimental; efficacy and safety in patients have not been established.

Following MI, EV-based therapies focus on reducing cardiomyocyte apoptosis, promoting angiogenesis and enhancing tissue repair. MSC-derived EVs regulate macrophage polarization through delivery of miR-182 during ischemia–reperfusion injury, thereby reducing inflammatory damage.²⁶ Hypoxia-conditioned MSC-EVs deliver miR-125b to inhibit cardiomyocyte apoptosis and preserve myocardial viability.¹⁰ Cardiosphere-derived-cell EVs reduce scarring and adverse remodeling in porcine MI models.¹¹ These findings support EVs as experimental cell-free regenerative therapies, but do not establish human efficacy.

In heart failure and pathological hypertrophy, EVs regulate intercellular communication between cardiomyocytes and fibroblasts. Fibroblast-derived EVs enriched with miR-21-3p induce cardiomyocyte hypertrophy and inhibition of this miRNA attenuates angiotensin II–mediated hypertrophy in experimental models.⁸ Patient-derived HF EVs with altered miR-21-5p have been associated with reduced regenerative potential in experimental assays; this observation does not demonstrate a therapeutic effect of MSC-EVs.¹³ Strategies to modulate EV cargo remain experimental and require disease-specific validation.

In atrial remodeling, extracellular-matrix-derived EVs promoted cardiomyocyte growth and altered electrical activity in engineered atrial tissue.³⁰ This finding does not establish a role for miR-21-3p or miR-199a-3p in clinical atrial enlargement or AF. Whether modifying these signals could affect human disease remains unknown.

In valvular heart disease, EVs have been implicated in calcification biology.^{31,32} The cited literature does not establish MSC-EV efficacy, engineered miRNA-EVs or targeted drug delivery in human valve disease. These approaches remain hypotheses for future preclinical investigation.

In hypertrophic and dilated cardiomyopathies, EV-based therapeutic strategies remain exploratory. The cited sources do not establish restoration of EV-associated miR-1/miR-133a in HCM or manipulation of miR-21-5p/miR-146a in DCM as effective therapies. Experimental EV approaches require disease-specific primary studies and clinical evaluation before therapeutic claims can be made.^{29,33,34,36,37}

In inflammatory cardiovascular conditions, EVs enriched with cytokines such as IL-6, TNF- α and CD14 have been proposed as indicators or mediators of intercellular inflammatory signaling.⁶ Therapeutic strategies aimed at modulating EV-mediated cytokine transfer or altering inflammatory EV cargo may attenuate vascular inflammation and affect cardiovascular outcomes, but clinical benefit has not been demonstrated (Table 2).

Challenges in clinical translation of extracellular vesicles

Although EV-based diagnostics and therapeutics have demonstrated considerable promise in cardiovascular medicine, several challenges continue to limit clinical translation. EV heterogeneity and variability in molecular cargo complicate reproducibility and inter-study comparability, while current isolation methods and uncertainties regarding biodistribution, immunogenicity, off-target effects, optimal dosing, scalable GMP-compliant manufacturing and standardized characterization remain important barriers.^{5,6,14,36} Preanalytical variables—including platelet activation during collection or processing, lipoprotein and protein co-isolation, anticoagulant, processing delay, centrifugation, storage and freeze–thaw history—can affect measured EV profiles. Differences in producer-cell source, culture conditions, purification, potency assays and dose normalization also contribute to heterogeneity across MSC-EV studies.^{5,14,36} Standardized reporting, multicentre validation and appropriate regulatory evaluation are needed to improve reproducibility and support clinical translation.

Current clinical trials and emerging therapeutic perspectives

Although EV-based therapies have demonstrated promising regenerative and anti-inflammatory effects in experimental cardiovascular models, clinical translation remains at an early stage. The registered SECRET-HF phase I study (NCT05774509) is evaluating intravenous administration of an EV-enriched secretome from induced-pluripotent-stem-cell-derived cardiovascular progenitor cells in 12 patients with nonischemic DCM.³⁸ A 2024 first-in-human report described feasibility and tolerability in the first treated patient; a single case cannot establish efficacy or safety across the planned cohort.³⁹ This product is not an MSC-EV preparation. Human EV biomarker studies are described in the diagnostic section and Table 3.^{15–18}

Overall, these early clinical studies emphasize the growing translational potential of EV-based diagnostics and therapeutics in cardiovascular medicine. These early investigations do not yet establish therapeutic efficacy in cardiovascular disease.

Current evidence does not establish that EV biomarkers detect cardiovascular disease before structural changes become visible on echocardiography. Prospective studies should determine whether EV assays add diagnostic or prognostic information to established biomarkers and imaging and whether that information improves clinical decisions. Large multicentre studies involving diverse populations and independent validation are needed before routine clinical use.

Conclusions

Cardiac function relies on coordinated communication between heart muscle cells (cardiomyocytes) and their nearby non-muscle partners. Recently, EVs have emerged as an important aspect in signaling between these cells, in both normal and abnormal heart function. Nevertheless, the mechanisms and clinical importance of EV signaling in cardiovascular health and disease remain incompletely understood.

EVs transport diverse bioactive cargo, including microRNAs, proteins, lipids and nucleic acids, that contribute to maintaining cardiovascular homeostasis. Alterations in EV cargo composition can promote the initiation and progression of cardiovascular diseases, highlighting their value as both biomarkers and therapeutic targets. This review emphasizes the growing diagnostic and therapeutic potential of EVs across a broad spectrum of cardiovascular disorders. Future advances in standardized

EV isolation and characterization methods, standardized collection and characterization, reproducible dose definition, independent validation and adequately powered multicentre clinical trials are expected to accelerate the clinical translation of EV-based diagnostics and therapeutics. Collectively, these developments have the potential to transform precision cardiovascular medicine by enabling earlier diagnosis, improved risk stratification and personalized treatment strategies for patients with cardiovascular diseases.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests: The authors declare that they have no competing interests.

Funding: No funding was received for this study.

Authors' contributions

Conceptualization: STR.

Investigation: RN.

Supervision: STR.

Visualization: RN.

Writing – Original Draft Preparation: RN.

Writing – Review & Editing: STR, WAA and FM.

Acknowledgements: The authors acknowledge the institutional support provided by Era's Lucknow Medical College and Hospital and Era University for facilitating academic resources and research infrastructure. No external funding was received for this work.

Use of artificial intelligence: Artificial intelligence (AI)-assisted tools (ChatGPT; OpenAI Large Language Model) were used for language refinement, grammar correction, figure creation and improvement of readability. AI was not used for data analysis, interpretation, scientific content generation or drawing conclusions.

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TABLES

Table 1. Cellular sources of extracellular vesicles in the cardiovascular system: cargo, target cells, functional effects and associated conditions.

EV source cell type	Key EV cargo (miRNAs / proteins)	Primary target cells	Functional effects	Associated cardiovascular conditions	Refs
Cardiomyocytes	Cargo varies with cell state and experimental model	Endothelial cells, fibroblasts, progenitor cells	Angiogenesis and remodelling reported in experimental studies; specific miRNA cargo should be assigned only when directly demonstrated	Myocardial infarction, heart failure	40
Endothelial cells / apoptotic endothelial-cell bodies	miR-126 in apoptotic bodies; miR-222; miR-503; miR-143/145	Endothelial cells, SMCs, pericytes, vascular smooth muscle cells	Source-specific vascular protection, ICAM-1 regulation, pericyte signalling and endothelial-to-smooth-muscle communication	Atherosclerosis, diabetes-related CVD	7, 22, 23, 25
Cardiac fibroblasts	miR-21-3p; ECM proteins	Cardiomyocytes	Induction of hypertrophy; experimental inhibition attenuates hypertrophic signalling	Cardiac hypertrophy, heart failure	8
Mesenchymal stromal cells (MSCs)	miR-125b; miR-182 (in separate studies)	Cardiomyocytes, macrophages	Reduced cardiomyocyte death or altered macrophage polarisation in preclinical models	MI, ischaemia–reperfusion injury	10, 26
Adipocytes / adipose tissue	Inflammatory EV cargo; no specific miRNA assigned in the cited study	Vascular endothelial cells, leukocytes	Promoted leukocyte attachment to vascular endothelium in experimental assays	Obesity-related vascular inflammation	41
Immune cells (monocytes / macrophages)	Cytokines; miRNAs; mitochondrial MT-CO1	SMCs, endothelial cells	Inflammation and SMC migration; clinical associations depend on the measured EV population	Atherosclerosis, CAD	12, 20

Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease; ECM, extracellular matrix; EV, extracellular vesicle; ICAM-1, intercellular adhesion molecule 1; MI, myocardial infarction; miR/miRNA, microRNA; MSC, mesenchymal stromal cell; MT-CO1, mitochondrially encoded cytochrome c oxidase I; SMC, smooth muscle cell.

Table 2. Extracellular vesicle (EV)-based therapeutic approaches across cardiovascular diseases: cargo, targets, mechanisms and level of evidence.

Cardiovascular disease	EV source	Key therapeutic cargo	Target cells	Principal mechanism	Evidence level	Refs
Myocardial infarction (MI)	MSC-derived EVs	miR-182	Macrophages	Alters macrophage polarisation and attenuates ischaemia–reperfusion injury	Preclinical animal models	26
	Hypoxia-conditioned MSC-EVs	miR-125b	Cardiomyocytes	Inhibits apoptosis; enhances myocardial survival	Preclinical	10
	Cardiosphere-derived cell EVs	Specific miRNA cargo not assigned	Cardiac tissue	Reduced scarring and adverse remodelling in porcine MI models	Preclinical animal models	11
Atherosclerosis / CAD	Apoptotic endothelial-cell bodies	miR-126	Endothelial cells	CXCL12-dependent vascular protection in experimental models	Experimental models	7
	KLF2-induced endothelial EVs	miR-143/145 signalling	Vascular smooth muscle cells	Atheroprotective endothelial-to-smooth-muscle communication	Animal studies	25
Heart failure (HF)	Patient-derived HF EVs / experimental EV models	miR-21-5p observations; therapeutic effect not established	Cardiomyocytes / recipient cells	Patient-derived HF EVs impaired regenerative potential in experimental assays; not evidence of MSC-EV therapy	Human observational source with experimental assays	13
Cardiac hypertrophy	Fibroblast-derived EV modulation	miR-21-3p inhibition strategy	Cardiomyocytes	Reduces hypertrophic signalling in angiotensin II models	Experimental	8
Valvular heart disease (VHD)	No validated EV therapy identified in cited sources	Specific therapeutic cargo not established	Valvular cells	EV involvement in calcification under study; therapeutic efficacy unestablished	Research direction; no demonstrated therapy	31, 32
Calcific aortic valve disease	Engineered EVs	miR-302/367, miR-29 and let-7 claims not established by cited primary sources	Valvular cells	No demonstrated inhibition of osteogenic pathways or valve-targeted delivery in cited evidence	Evidence gap	31

Cardiovascular disease	EV source	Key therapeutic cargo	Target cells	Principal mechanism	Evidence level	Refs
Dilated cardiomyopathy (DCM)	MSC / endothelial progenitor EVs	VEGF; FGF; antioxidant enzymes	Cardiomyocytes; endothelial cells	General preclinical regenerative hypotheses; disease-specific efficacy not established	Preclinical; not established for DCM	36, 37
Hypertrophic cardiomyopathy (HCM)	Cardiomyocyte-derived EV modulation	miR-1; miR-133a restoration claims not established as therapy	Cardiomyocytes	No disease-specific therapeutic effect established	Evidence gap	6, 35

Abbreviations: CAD, coronary artery disease; CXCL12, C-X-C motif chemokine ligand 12; DCM, dilated cardiomyopathy; EV, extracellular vesicle; FGF, fibroblast growth factor; HCM, hypertrophic cardiomyopathy; HF, heart failure; KLF2, Krüppel-like factor 2; MI, myocardial infarction; miR/miRNA, microRNA; MSC, mesenchymal stem/stromal cell; VEGF, vascular endothelial growth factor; VHD, valvular heart disease.

Table 3. Selected clinical studies of extracellular vesicle (EV)-associated biomarkers in cardiovascular disease: cohorts, methods, reported performance and validation status.

Disease / cohort	Biofluid	Isolation and characterisation	EV marker / candidate	Reported performance	Validation and interpretation	Refs
Acute MI / stable angina / controls; training n = 98 (30/38/30), validation n = 80	Serum	EV concentration by NTA; surface epitopes by flow cytometry	EV concentration, CD62P and CD42a	AUC 0.969 for STEMI vs controls in training; non-inferiority to troponin reported	Separate validation cohort; clinical utility and broad external transportability not established	15
HFmrEF; n = 74; 13 with systolic progression	Plasma	Flow cytometry; CD45+ leukocyte EV subset	CD45+ leukocyte EV concentration	AUC 0.70 (95% CI 0.54–0.85); sensitivity 75.0%; specificity 58.3%	Prospective multicentre cohort; no independent external validation reported; incremental value over NT-proBNP not established	16
Subclinical coronary atherosclerosis; n = 16 discovery, n = 34 validation	Plasma	EV enrichment; TEM, total protein, CD63/CD9 immunoblot; miRNA array and RT-qPCR	miR-146b-5p, miR-4701-3p, miR-1180-3p panel	AUC 0.8281; sensitivity and specificity 93.75% in validation	Independent validation sample; external-site validation and standard biomarker comparison not established	17
Post-ACS prognosis; main cohort n = 4541; fractionation subset n = 27	Plasma	Main cohort: extracellular miRNA; EV and non-vesicular fractions assessed in separate subset	miR-223-3p and miR-378c	Adjusted Q4 HRs 0.61 (95% CI 0.43–0.85) and 1.39 (0.97–1.98) for HF hospitalisation/CV death	Main cohort associations are not EV-specific; particle localisation in n = 27 subset; EV-specific HR not established	18

Abbreviations: ACS, acute coronary syndrome; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CV, cardiovascular; EV, extracellular vesicle; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HR, hazard ratio; MI, myocardial infarction; miR/miRNA, microRNA; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NTA, nanoparticle tracking analysis; Q4, fourth quartile; RT-qPCR, reverse transcription quantitative PCR; STEMI, ST-segment elevation myocardial infarction; TEM, transmission electron microscopy.

Figures

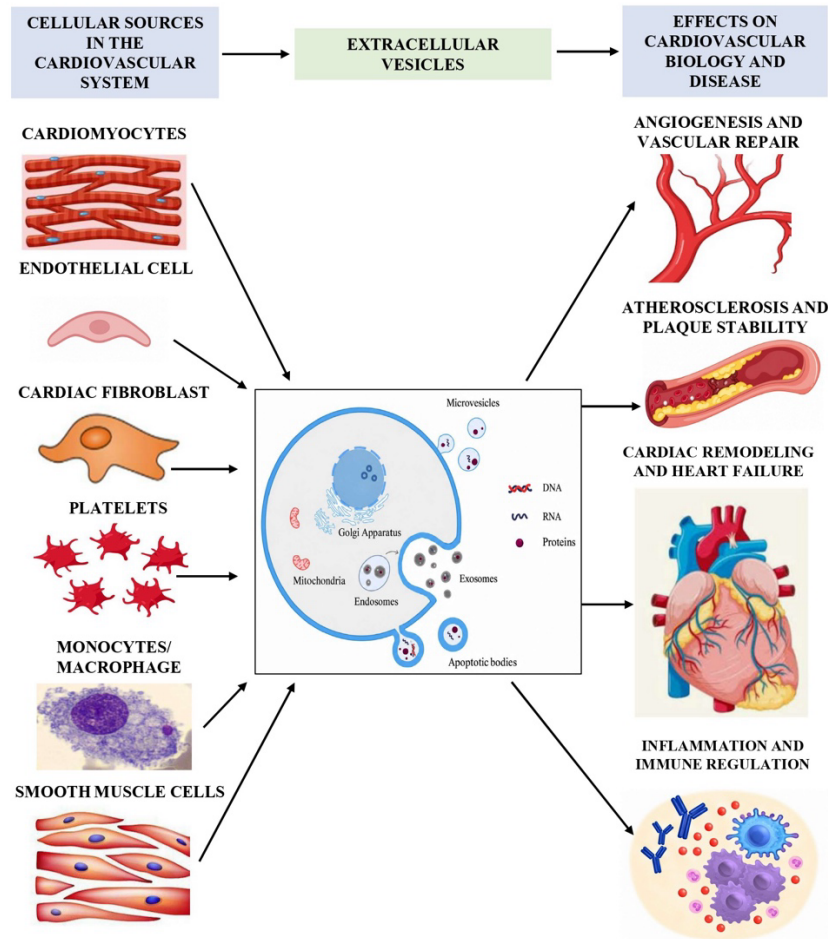


Figure 1. Cellular sources, biogenesis, and cardiovascular effects of extracellular vesicles (EVs). **Left:** Cardiomyocytes, endothelial cells, cardiac fibroblasts, platelets, monocytes/macrophages, and smooth muscle cells release EVs. **Center:** Exosomes are released when multivesicular bodies fuse with the plasma membrane. Microvesicles bud directly from the plasma membrane, and apoptotic bodies are shed from apoptotic cells. EVs carry proteins, lipids, and nucleic acids. **Right:** EVs influence angiogenesis, atherosclerosis, cardiac remodeling, and inflammation, with beneficial, neutral, or adverse effects depending on biological context.

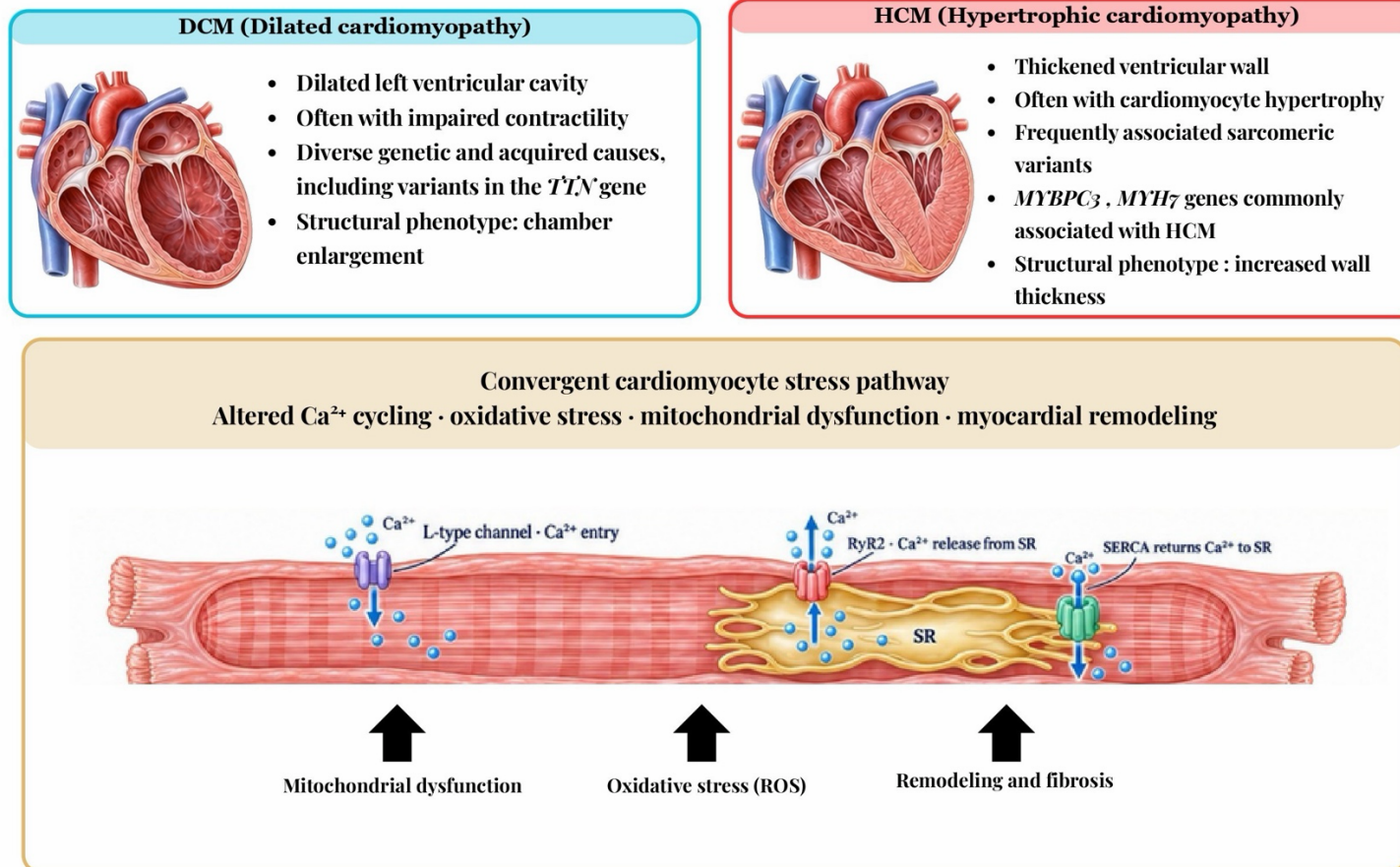


Figure 2. Structural phenotypes of dilated and hypertrophic cardiomyopathy and their convergent cardiomyocyte stress pathways. **Top:** Dilated cardiomyopathy (DCM; left) is characterized by left ventricular cavity enlargement and impaired contractility. It has diverse genetic and acquired causes, including variants in *TTN*. Hypertrophic cardiomyopathy (HCM; right) is characterized by increased ventricular wall thickness and cardiomyocyte hypertrophy. It is frequently associated with sarcomeric gene variants, most commonly in *MYBPC3* and *MYH7*. **Bottom:** Despite their distinct structural phenotypes, both conditions converge on shared cardiomyocyte stress pathways. Excitation–contraction coupling is shown schematically. Ca^{2+} enters through L-type Ca^{2+} channels, which triggers Ca^{2+} release from the sarcoplasmic reticulum (SR) via ryanodine receptor 2 (RyR2). The SR Ca^{2+} -ATPase (SERCA) then returns Ca^{2+} to the SR. Mitochondrial dysfunction, oxidative stress from reactive oxygen species (ROS), and myocardial remodeling and fibrosis disrupt Ca^{2+} handling and contribute to disease progression.