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REVIEW ARTICLE

Advances in Cardioprotective Strategies: Bridging Traditional Pharmacotherapy and Regenerative Medicine

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Abstract

Cardiovascular diseases (CVDs) remain the leading global cause of death and disability, underscoring the need for improved therapies. Key emerging strategies include pharmacological cardioprotection, cell-based therapies and the use of exosomes as therapeutic agents and biomarkers. Aim of this study was to characterise contemporary approaches to cardioprotection in CVDs, including pharmacological agents, cell-based therapies and exosome-based strategies, based on an analysis of evidence-based data. A systematic literature search was performed using databases including *PubMed, Clinical Key (Elsevier), Cochrane Library, eBook Business Collection* and *Google Scholar*. Keywords included cardioprotection, exosomes, cell-based therapies and pharmacological approaches. Article selection followed evidence-based medicine principles and the PRISMA guidelines. Current cardioprotective strategies include both traditional pharmacological agents, such as β-blockers, calcium channel blockers, ACE inhibitors, statins and nitrates, as well as innovative approaches like cell-based therapies and the use of exosomes. The advantages and limitations of cell therapy were analysed, including challenges related to low cell survival, failure of differentiation and the risk of arrhythmias. The role of exosomes and microvesicles as promising markers of cardiovascular injury and potential therapeutic agents was also explored. Combining pharmacological, cell-based and exosome-based strategies offers new prospects for cardioprotection in CVDs. Further research is required to optimise the clinical use of cell therapies and to confirm the efficacy of exosome-based interventions.

Key words: Cardiovascular diseases; Prevention and control, cardiac; Exosomes; Cell and tissue-based therapy; Therapeutics; Ischaemia; Ischaemic injury; Regenerative medicine; Adrenergic beta-antagonists; Calcium channel blockers; Microvesicles.

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Introduction

Cardiovascular diseases (CVDs) are the leading cause of global mortality and disability. They include a range of conditions, with atherosclerosis, ischaemic heart disease (IHD), acute cerebrovascular accidents, cardiomyopathies and heart failure (HF) being particularly significant.[1] These conditions often coexist and their pathogenesis is closely interconnected, substantially complicating diagnosis and treatment.[2]

The primary risk factors for CVD development include cardiometabolic, behavioural, environmen-

tal and social determinants, which interact to promote the onset and progression of cardiovascular pathology. Globally, the prevalence of these risk factors has led to a continuous rise in CVD burden. From 1990 to 2019, the number of people living with CVD grew from 271 million to 523 million, while CVD-related deaths increased from 12.1 million to 18.6 million.[1] These trends highlight the ongoing rise in CVD incidence and mortality globally. The prevalence of CVDs is expected to grow, driven mainly by population growth and aging, particularly in regions like Northern Africa, Latin America, the Caribbean and Southeast Asia. The proportion of elderly individuals in these regions is expected to double by 2050, placing increased pressure on healthcare systems.[3]

The COVID-19 pandemic, which began in 2019, has added another layer of complexity to global health challenges. More than seven million deaths have been reported and millions more individuals have suffered significant health impairments. Although vaccination programs have substantially reduced mortality and hospitalisation rates, the cardiovascular consequences of COVID-19 remain a pressing concern. Many post-infection patients experience persistent cardiac symptoms, often without clear objective findings, complicating both diagnosis and management. Moreover, the lack of adequately matched control groups and insufficient data for developing effective therapeutic strategies further emphasises the urgency of addressing these issues.[4]

Contemporary IHD management includes percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), pharmacotherapy and non-pharmacological approaches. PCI and CABG are highly effective in improving myocardial perfusion, alleviating symptoms and enhancing quality of life. Concurrently, conservative treatment strategies, particularly pharmacotherapy, play a critical role in controlling atherosclerosis progression and preventing atherothrombotic events. Combination therapy, including anti-ischaemic agents (β-blockers, calcium channel blockers), antiplatelet therapy (aspirin, clopidogrel) and lipid-lowering agents (statins), manages IHD symptoms, reduces event risk and slows disease progression.[5–7]

Given the limitations of conventional therapies, there is growing interest in regenerative approaches for myocardial repair, particularly in advanced cardiovascular disease. Stem cell-based therapies, owing to their differentiation, regenerative and immunomodulatory properties, offer promising prospects for cardiology. Studies have shown that stem cells can promote myocardial regeneration after infarction and improve outcomes in heart failure patients.[2] These innovative strategies can potentially radically reshape treatment approaches and significantly improve prognosis in individuals with severe cardiac pathology.

Aim of this study was to characterise contemporary approaches to cardioprotection in cardiovascular diseases, with particular emphasis on pharmacological agents, cell-based therapies and exosome-based strategies, based on the analysis of evidence-based data.

Data collection

A comprehensive search of the literature was carried out across multiple databases, including PubMed, *Clinical Key Elsevier*, *the Cochrane Library*, *the eBook Business Collection* and *Google Scholar*, using keywords like "cardioprotection," "exosomes," "cell-based therapies," and "pharmacological approaches." Studies were selected following established guidelines for systematic reviews. The process was divided into three stages: First, relevant literature was identified using keywords such as Cardioprotection, Pharmacotherapy, Stem Cells, Exosomes, Cardiovascular Diseases and Regenerative Medicine. Second, abstracts were reviewed and studies that did not meet the inclusion criteria were excluded. Finally, full-text articles were examined to assess their relevance and compliance with the inclusion criteria. Inclusion criteria comprised the recency of data (preferably within the last five years), open access to full-text articles and scientific relevance to the topic of cardioprotection in cardiovascular diseases.

Cardioprotective agents: classification, mechanisms of action and their role in clinical practice

Cardioprotective agents are specialised pharmacological and biologically active substances capable of reducing the risk of myocardial injury, improving metabolic processes within cardiomyocytes and facilitating cardiac adaptation to stressful conditions.[2, 5, 6, 8] The modern approach to cardioprotection relies on the established understanding of underlying molecular mechanisms of action of cardioprotective agents (Table 1) and includes the application of innovative technologies that contribute to quality of life and increasing long-term survival.[8]

Cardioprotection research is advancing rapidly. Gene therapy and nanotechnology are considered promising directions in this area. Genetic approaches enhance cardiac cell stress resistance through targeted modulation of intracellular signalling. Nanotechnologies provide targeted delivery of cardioprotective agents to damaged myocardial areas, significantly improving therapeutic efficacy and minimising side effects. This opens new opportunities for treating cardiovascular diseases and developing therapies based on innovative technologies.

β-adrenergic receptor blockers

β-blockers exert key cardioprotective effects by reducing myocardial oxygen and energy substrate demand through negative inotropic and chronotropic actions, prolonging diastolic perfusion and lowering intracellular calcium concentrations. Additionally, they restore β-adrenergic receptor affinity to catecholamines in states of hypercatecholaminaemia common in cardiovascular diseases.[9]

Randomised controlled trials have shown that β-blockers reduce mortality and improve cardiac function. Recent research focuses on developing more selective agents with reduced pulmonary and metabolic side effects, thereby broadening their clinical use.[10–12]

In the perioperative setting, β-blocker continuation is recommended for patients with existing cardiovascular disease. However, a large cohort study (11,875 patients, 2018) questioned their preoperative initiation, showing increased risks of mortality, stroke and myocardial infarction. Initiating β-blocker therapy in low-risk patients may impair compensatory hemodynamic responses to blood loss, highlighting the need for further studies to define optimal perioperative indications.[10–12]

Calcium channel blockers

Calcium channel blockers (CCBs) improve myocardial perfusion, reduce cardiac energy expenditure and optimise oxygen consumption by limiting calcium influx. They decrease vascular smooth muscle tone, lower peripheral resistance

Table 1: Key pharmacological groups of cardioprotective agents[8]

Agents predominantly targeting energy processes	Antioxidant agents and electron acceptors	Inhibitors of free fatty cid oxidation	ATP-sensitive K^+ channel openers
Phosphocreatine	Quercetin	L-carnitine (Levocarnitine)	Nicorandil
Magnesium gluconate	Lecithin	Trimethylhydrazinium propionate	
Potassium gluconate	Thiotriazoline	Trimetazidine hydrochloride	
Carbonate	Niacin	Ranolazine	
Taurine	L-arginine monohydrate		
Meldonium	Ceruloplasmin		
Sodium adenosine triphosphate	Methylethylpyridinol		
	Ethylmethylhydroxypyridine succinate		
	Ubiquinone		
	Cytochrome oxidase		

and enhance blood flow, benefitting patients with hypertension and ischaemic heart disease.[9]

While CCBs show potential for reducing ischaemia-reperfusion myocardial injury (IRMI), clinical evidence remains inconclusive, necessitating further investigation. These agents also lower heart rate, decreasing myocardial workload and improving cardiac function, which supports their role in managing heart failure. Future studies are essential to clarify their impact on IRMI and long-term cardiovascular outcomes.[12–14]

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)

ACEIs and ARBs are key therapies for hypertension and chronic heart failure, improving ventricular filling, reducing arrhythmias and mitigating reperfusion injury.[9] Their cardioprotective effects stem from preventing left ventricular hypertrophy and remodelling, enhancing myocardial function and exerting vascular protective actions by inhibiting smooth muscle proliferation. In the perioperative period, ACE-Is and ARBs lower peripheral resistance and improve left ventricular function, although intraoperative use may provoke hemodynamic instability, warranting careful timing of discontinuation.

Levosimendan, a novel calcium sensitiser, offers potent inotropic support and moderate vasodilation, improving hemodynamics and reducing myocardial oxygen demand. However, it requires careful monitoring due to risks of hypotension and tachycardia.[11, 15–17]

Diuretics

Diuretics remain essential for managing cardiovascular diseases, particularly CHF. Thiazide diuretics effectively reduce blood volume and blood pressure in early hypertension, while loop diuretics like furosemide address more severe heart failure and oedema.[9]

Appropriate diuretic use prevents complications such as pulmonary oedema and heart failure exacerbations, improving quality of life and reducing hospitalisations. Continuous monitoring is necessary to minimise adverse effects and ensure safe treatment.[18, 19]

Statins

Statins are pivotal in modern cardiology for reducing the risk of major cardiovascular events. Beyond their lipid-lowering properties, they exert anti-inflammatory and antioxidant effects, stabilise atherosclerotic plaques, enhance endothelial function and promote nitric oxide synthesis, contributing to vasodilation and blood pressure reduction.[9] Their multifaceted actions underscore their role in preventing myocardial infarction, stroke and atherosclerotic disease progression.

Nitrates

Nitrates play a critical role in alleviating acute myocardial ischaemia symptoms. Nitroglycerin reduces preload and afterload, lowers myocardial energy demand and improves subendocardial perfusion by decreasing left ventricular diastolic pressure.

Additionally, nitrates relieve coronary artery spasms, a key trigger of acute ischaemic events and reduce platelet aggregation via nitric oxide-mediated pathways, enhancing endothelial function.[20, 21] The combination of these pharmacological agents provides a comprehensive approach to managing cardiovascular diseases. Therapy should be tailored to individual patient factors and comorbidities. Ongoing refinement of existing therapies and development of new agents promise improved cardiovascular outcomes.

Specific aspects of cardioprotection in the perioperative period

Myocardial ischaemia-reperfusion injury (IRI) in the postoperative period is a complex, multifactorial process, involving disturbances in oxygen supply-demand balance even in patients with anatomically normal coronary arteries.[22, 23]

Factors contributing to ischaemic imbalance include significant coronary stenoses, coronary artery spasms, microvascular dysfunction and embolisation, as well as increased myocardial oxygen consumption.[9] Additional perioperative triggers include tachyarrhythmias, hypertension or hypotension, bradyarrhythmias impairing

cardiac output and hypoxaemia, all exacerbating myocardial ischaemia. [24–26]

Other contributors such as severe anaemia, coronary vasospasm, electrolyte imbalances, acidosis and shock further elevate the risk of type 2 myocardial infarction. Therefore, meticulous monitoring and management of these variables are critical for optimising myocardial perfusion, facilitating recovery and preventing serious postoperative complications.

Halogenated inhalational anaesthetics

Modern inhalational anaesthetics, notably sevoflurane and desflurane, offer cardioprotection through anaesthetic preconditioning, attenuating apoptotic pathways during reperfusion. Their dose-dependent haemodynamic effects — reduced afterload with preserved contractility and improved diastolic function — facilitate myocardial adaptation to surgical stress. However, clinical evidence remains mixed, influenced by patient and procedural factors.[27, 28] Current guidelines support their use in hemodynamically stable patients with IHD and preserved ejection fraction.

α2-adrenergic receptor agonists

α2-adrenergic receptor agonists may provide cardioprotection by decreasing heart rate, lowering blood pressure and reducing oxygen consumption, while promoting coronary vasodilation via nitric oxide and adenosine. They also possess anti-inflammatory, antioxidant and antiapoptotic properties. Dexmedetomidine, a newer agent, shows promise but requires further validation. While early studies suggested a reduction in perioperative myocardial infarctions, later meta-analyses found no decrease in mortality or ischaemic events and confirmed increased risks of bradycardia and hypotension.[29–31] Thus, α2-agonists are currently not recommended for perioperative cardioprotection.

Non-pharmacological cardioprotection and limitations of cell therapy

Decades ago, it was found that cardiomyocytes have signalling pathways that protect against ischaemia-reperfusion injury, a mechanism known as “cardioprotection”.[32–34] Cardioprotection can be induced by ischaemic preconditioning and postconditioning of the myocardium.[32] While highly protective, these methods involve ischaemia-reperfusion, which carries risks like atherosclerotic damage and microembolisation, especially during postconditioning. Alternatively, cardioprotection can be induced through brief ischaemia-reperfusion at remote non-cardiac sites (remote ischaemic conditioning).[32, 35]

Table 2: Characteristics of cell sources for therapeutic cardiac regeneration (adapted from[37])

Generation	Cell type	Source	Markers	Advantages	Limitations	References
First generation	**Bone marrow and peripheral blood progenitor cells**	Bone marrow, Peripheral blood	$CD117^+$, $CD34^+$	Limited regenerative potential; Phase 3 trials; Minimal cardiac function improvement, limited engraftment; Easy cryopreservation; Genetically modifiable; Safe; Accessible; No ethical or immunological issues; Extensive clinical experience	Limited differentiation potential; Limited yield	38–52

First generation	**Mesenchymal stem cells**	Embryonic, adult tissues, tooth germ	CD105$^+$, CD117$^+$	Limited regenerative potential; Phase 3 trials; Minimal cardiac function improvement, limited engraftment; Easy cryopreservation; Genetically modifiable; Safe; Accessible; Source of paracrine factors	Limited differentiation potential; Yield-dependent	53
	Side population cells	Heart biopsy	Abcg2$^+$, Mdr1$^+$	Limited regenerative potential; No clinical strategy	Limited yield	54–56
	Epicardial progenitor cells	Heart development	Wt1$^+$, Tbx18$^+$, CD90$^+$, CD44$^+$	Limited regenerative potential; No clinical strategy	Limited yield	57–60
	Isl+ progenitor cells	Heart development	Isl1$^+$	Limited regenerative potential; No clinical strategy	Limited yield	61–63
Second generation	**Cardiosphere-derived cells**	Heart biopsy	c-kit$^+$, Sca-1$^+$, CD105$^+$, CD29$^+$, CD45$^-$	High regenerative potential; Phase 1–2 trials; Improved cardiac function; Limited engraftment	Limited yield	64
	c-kit	Heart biopsy	c-kit$^+$, CD45$^-$	High regenerative potential; Phase 2 trials; Improved cardiac function; Limited engraftment	Limited yield	65–68
	Sca-1	Heart biopsy	c-kit$^+$, CD31$^+$, CD14$^-$, CD34$^-$, CD105$^+$, CD45-	High regenerative potential; Preclinical stage; Limited engraftment	Limited yield	69–71
	Embryonic stem cells	Blastocyst inner mass	Oct4$^+$, Nanog$^+$, SSEA4$^+$	High regenerative potential; Preclinical; Phase 1 trials	Ethical concerns; Teratoma formation; Immunogenicity	72
	Induced pluripotent stem cells	Reprogrammed somatic cells	Oct4$^+$, Nanog$^+$, SSEA4$^+$	High regenerative potential; Preclinical stage; Improved cardiomyocyte differentiation	Tumorigenicity	73–76

An alternative approach involves attempting to regenerate lost myocardium or improve myocardial function. However, due to the terminal differentiation of mammalian cardiomyocytes, spontaneous myocardial regeneration through cell proliferation is extremely limited. Therefore, efforts have focused on myocardial regeneration via the injection of various stem cell types.[36] Yet, the biological activity of transplanted cells varies significantly depending on cell source, preparation and delivery methods (Table 2).

Cell therapy holds significant potential for treating cardiovascular diseases (CVD), but its clinical implementation faces several important challenges. Key obstacles include poor engraftment, low survival of transplanted cells and inefficient cell differentiation. Additionally, minimising the risk of adverse effects, such as arrhythmias following cell therapy, remains critical. To establish cell therapy as a standard treatment, these challenges must be addressed through further research. A detailed analysis of these aspects is provided below.[37]

Low engraftment of bone marrow and blood-derived endothelial progenitor cells

Cell therapy is limited by poor engraftment, as few transplanted cells survive and contribute to repair—mainly due to insufficient blood supply in ischaemic tissue.[77–79]

Poor viability of transplanted cells in ischaemic tissues

Ischaemic areas often lack sufficient blood supply, leading to tissue damage and impaired organ function. Transplanted cells suffer from oxygen and nutrient deprivation, resulting in high rates of cell death. Additionally, insufficient removal of metabolic waste products further compromises cell viability.[80]

Limited differentiation of adult stem cells into functional heart cells

A key aim of cell therapy is to generate mature cardiomyocytes that repair damaged heart tissue. However, poor differentiation—due to inadequate induction or hostile tissue environments—often limits its effectiveness.[81]

Limited recruitment of circulating or resident cardiac stem cells

Another key issue is the insufficient recruitment of cardiac stem cells to the injured myocardium. Both circulating and resident stem cell pools are often inadequate, with impaired activation mechanisms limiting their availability for therapy.[82]

Abnormal electromechanical coupling leading to arrhythmias

One serious risk of cell therapy is the disruption of normal cardiac electrical activity due to abnormal coupling between transplanted and native cells. This can trigger dangerous arrhythmias and represents a major safety concern.[83]

Limitations of left ventricular ejection fraction (LVEF) as an indirect marker in assessing cell therapy

LVEF is commonly used to assess the effectiveness of cell therapy. However, because it is highly load-dependent, it may not reliably reflect true myocardial recovery. Changes in preload and afterload can mask actual improvements in contractility.[84]

Inappropriate selection of patient population

Another limitation is the selection of patients with relatively preserved cardiac function, such as those with baseline LVEF around 50 %, who may not benefit significantly from cell therapy.[84]

Availability of well-developed alternative therapeutic strategies

Several established interventions, such as percutaneous coronary intervention, fibrinolysis, ACE inhibitors and β-blockers, may offer better or comparable outcomes, reducing the relative need for cell therapy.[85]

Lack of experimental validation of cell preparations during clinical trials

Many trials lack robust experimental validation of cell preparations, leading to inconsistent results and raising concerns about the reproducibility and standardisation of therapies. Thus, despite some promising results in preserving myocardium and improving cardiac function, cell therapy for CVD has not yet succeeded in increasing the number of cardiomyocytes. Recently, attention has shifted toward factors secreted by stem cells that may mediate paracrine effects. Among these, exosomes have emerged as a promising mediator of therapeutic effects.[36]

Exosomes and microvesicles as biomarkers in cardiovascular disease

Nearly all cardiovascular cells release small lipid vesicles called exosomes. Though their isolation and analysis remain technically challenging, exosomes from different sources have shown strong cardioprotective properties.[36] Extracellular vesicles (EVs), particularly exosomes, play a paracrine role by releasing into the extracellular space and inducing anti-apoptotic, angiogenic, immunomodulatory and anti-fibrotic responses.[87,88]

Table 3: Molecular components of exosomes (adapted from[87])

Type	Category	Examples	References
Proteins	Tetraspanins	CD9, CD37, CD53, CD55, CD63, CD81, CD82	96, 97
	Cytoskeletal proteins	Actin, tubulin, cofilin-1, moesin, myosin, vimentin, ezrin, radixin, perlecan, fibronectin, THBS1, IQGAP1, keratin	96– 98
	Tetraspanins	CD9, CD37, CD53, CD55, CD63, CD81, CD82	96, 97
	Biogenesis proteins	ESCRT-0, I, II, III, Her, Vps4, TSG101, Alix, flotillin, clathrin	98
	Transport and synthesis	RAS-related proteins 5 and 7, annexins I–VI, dynamin, syntaxin-3, RAB4, RAB5, RAB7, RAB11, RAP1B, RABGDI, SLC3A2, CLIC1	96–98
	Heat shock proteins	αB-crystallin, HSP20, HSP22, HSP27, HSP40, HSP60, HSP70, HSP90, HSC70, HSPA5, CCT2	96, 98, 99
	Adhesion molecules	ICAM-1, integrins, lactadherin, MFGE8, P-selectin	96, 97
	Antigen presentation	Human leukocyte antigens class I and II	96
	Signaling proteins	GTPase, HRAS, syntenin-1, Gi2a, 14-3-3 proteins, ARF1, CDC42, NRAS, EHD1, EHD4, RAN, PEBP1, MIF, RRAS2, stomatin, PDCD6	96– 98
	Transport	Transferrin receptor	96
Enzymes	Glycosylation and metabolism	Glucose-6-phosphate isomerase, fatty acid synthase, GAPDH, PFKL, peroxiredoxin-1, hexokinase, PGK1, PGAM1, pyruvate kinase M1/M2, ATP-citrate lyase, ATPase, AST, aldehyde reductase, enolase-1, LDH, aldolase-1, DPP-4	96– 98, 100
Cytokines	Anti-inflammatory proteins	Tumor necrosis factor-alpha (TNF-α)	96
Anti-apoptotic	Apoptosis regulators	Alix, thioredoxin peroxidase	97
Transcriptional regulators	Transcription factors	EEF1A1, EEF2, LGALS3, EEF1A2	98
Caveolae	Caveolin-related proteins	Caveolin-1, caveolin-3	101
Lipids	Phospholipids	Phosphatidylcholine, phosphatidylserine, lysophosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, lysobisphosphatidic acid	102
	Cholesterol	—	102
	Ceramides	—	102, 103
	Sphingolipids	Sphingomyelin, hexosylceramide, lactosylceramide	97
	Gangliosides	GM1, GM3	104, 105
	Other lipids	Arachidonic acid, prostaglandin E, 15-d-PGJ2, diacylglycerol, triacylglycerol, hexadecylglycerol	102, 106

Nucleic acids	RNA	miRNAs (Let-7, miR-1, miR-15, miR-16, miR-17, miR-18, miR-19b, miR-20, miR-21, miR-29a, miR-126, miR-143, miR-145, miR-151, miR-155, miR-181, miR-200, miR-214, miR-320, miR-375, miR-382)	96, 102
	Other RNA types	mRNA, circRNA, mitochondrial RNA, tRNA, spliceosomal RNA, precursor RNA	96, 107
	DNA	DNA, viral DNA	107

The term *exosome* was originally introduced in 1981 to describe submicron lipid vesicles secreted by cells.[89] It was later defined more specifically as vesicles 50–150 nm in size, containing transferrin receptors and released by maturing blood reticulocytes.[90] Exosomes carry RNA and soluble proteins and display surface receptors that target specific recipient cells. The RNA cargo includes both mRNA and microRNA (miR), capable of modulating gene expression in recipient cells.[91]

EVs include microvesicles and exosomes. Microvesicles (100–1000 nm) are shed from the plasma membrane and carry bioactive molecules like proteins, lipids and RNA. Exosomes (30–150 nm) originate from intracellular organelles and contain RNA and proteins in a lipid membrane. The plasma of healthy individuals contains about 10^{10} EVs per millilitre.[92, 93] All cell types, including platelets, erythrocytes, lymphocytes, endothelial cells and parenchymal cells, contribute to the EV pool.[86]

Although exosomal content shares similarities with other EV types, analytical studies have revealed distinct molecular components (Table 3),[94] which often vary by the originating cell type.[95]

Microvesicles and exosomes are implicated in various cardiovascular conditions, involving endothelial dysfunction and coagulopathies. Elevated levels of endothelial-derived microvesicles with procoagulant properties have been identified in patients with acute coronary syndrome.[108] Assessing endothelial microvesicles may aid in identifying patients at risk for coronary artery disease.[109] Platelet-derived EVs have a dual role, being both prothrombotic and angiogenic. While they can promote clot formation, they also stimulate angiogenesis in ischaemic tissues. In a rat model of chronic myocardial ischaemia, platelet microvesicles increased functional capillaries. Following vascular injury, activated platelets release EVs, including exosomes and microvesicles.[110-113] Platelet-derived EVs interact with angiogenic cells, modulating SDF-1α/CXCR4 signalling to enhance their maturation and re-endothelialisation.[86, 114]

Cardiomyocytes release exosomes and cardiac fibroblasts, which make up most non-myocyte cardiac cells, influence myocardial function through signalling molecules. Exosomes from fibroblasts, containing microRNAs like miR-21, can induce cardiomyocyte hypertrophy by targeting specific genes. Inhibiting miR-21 reduced hypertrophy in a cardiac injury model, emphasising the role of fibroblast-derived exosomes in this process.[115-118] Non-coding RNAs (RNAs), which make up 98 % of RNA in the body, include ribosomal RNA, transfer RNA, microRNA, long non-coding RNA and circular RNA. MicroRNA regulates gene expression by binding to messenger RNA, causing degradation or repression. Long non-coding RNA and circular RNA affect gene expression through epigenetic and translational mechanisms. Given their role in regulating signalling pathways, non-coding RNAs are being explored as potential therapeutic agents with systemic delivery strategies.[119-121]

Current methods for diagnosing acute myocardial infarction (AMI) rely on detecting proteins like cardiac troponin, which are released during cardiomyocyte necrosis. Necrosis can also release protein-bound miRNAs into the bloodstream. However, exosomes, actively secreted by injured cells, offer the potential for earlier and more specific pre-necrotic identification. Released within minutes of infarction, these vesicles carry a complex cargo, including miRNAs, mRNAs, lncRNAs and proteins, offering a potential molecular fingerprint of infarction.[91]

Therapeutic potential of exosomes as an alternative to stem cell therapy

Exosomes, known for decades, show promise in regenerative medicine, particularly for cardiac diseases. While simpler than cell therapies, exo-

some-based treatments may have limited efficacy and require further clinical research to determine their potential in cardiovascular disease. Exosomes, despite not being living organisms, contain proteins and can be classified as biological medicinal products or advanced therapy products, depending on their source. A regulatory framework for EVs has been proposed by ISEV, with exosomes potentially commercialised as cell manufacturing by-products.[122, 123]

Clinical trials on EVs for cardiac conditions are in early stages. The EV-AMI trial is testing exosome infusion for AMI safety, while another Iranian study explores mesenchymal stem cell (MSC)-derived exosomes and mitochondria in coronary artery bypass grafting (CABG). A French study is assessing the safety and efficacy of EVs from cardiac progenitor cells in severe heart failure. These trials aim to address safety, but challenges remain, especially with repeated EV administrations.[124]

MSC-derived exosomes influence atherosclerosis by regulating macrophage polarisation via the miR-let7/HMGA2/NF-κB pathway, promoting the anti-inflammatory M2 phenotype and reducing inflammation. They also decrease macrophage infiltration into plaques by inhibiting the miR-let7/IGF2BP1/PTEN axis, limiting macrophage survival. Additionally, miR-129-5p in MSC-derived exosomes reduces cardiac inflammation and improves heart function. Exosomes from endothelial progenitor cells (EPC-Exos) prevent myocardial fibrosis. While MSC-derived exosomes show strong cardioprotective effects, challenges remain in standardising production, understanding their interactions with cardiac tissues and ensuring long-term safety in clinical applications.[125-132]

Conclusion

- While traditional drugs (eg, β-blockers, statins) provide substantial clinical benefits in managing cardiovascular diseases, they are insufficient in fully preventing myocardial remodelling and heart failure progression, especially in high-risk patients.
- Stem cell-based approaches for myocardial regeneration face challenges such as low cell survival, limited engraftment, incomplete differentiation and arrhythmogenic risks. Clinical outcomes remain variable and require validation in large-scale trials.
- Exosomes offer a promising, cell-free alternative for cardiac repair due to their anti-inflammatory, pro-angiogenic and anti-apoptotic properties. They hold potential as biomarkers for early myocardial injury, though issues such as standardised production and long-term safety need resolution.
- The future of cardioprotection lies in combining pharmacotherapy with regenerative and nanotechnology-based strategies. Personalised medicine, driven by molecular diagnostics and targeted delivery, will further enhance therapeutic outcomes.
- Further multidisciplinary research is required to overcome current challenges and translate exosome-based and regenerative therapies into standard clinical practice, ultimately improving patient outcomes in cardiovascular disease.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al; Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990–2019. J Am Coll Cardiol. 2020;76(25):2982–3021. doi: 10.1016/j.jacc.2020.11.010.
2. Bakinowska E, Kiełbowski K, Boboryko D, Bratborska AW, Olejnik-Wojciechowska J, Rusiński M, et al. The role of stem cells in the treatment of cardiovascular diseases. Int J Mol Sci. 2024 Mar 31;25(7):3901. doi: 10.3390/ijms25073901.
3. United Nations, Department of Economic and Social Affairs, Population Division. World population ageing 2019: highlights. ST/ESA/SER.A/430. [Internet]. New York: United Nations; 2019 [Cited:30-Apr-2025]. Available from: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WorldPopulationAgeing2019-Highlights.pdf.
4. Gandhi RS, Raman B. The complexity of cardiovascular long COVID: where we are. Cardiovasc Res. 2024 Jul 2;120(8):e30–e32. doi: 10.1093/cvr/cvae090.
5. Liao R, Li Z, Wang Q, Lin H, Sun H. Revascularization of chronic total occlusion coronary artery and cardiac regeneration. Front Cardiovasc Med. 2022 Aug 25;9:940808. doi: 10.3389/fcvm.2022.940808.
6. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407–477. doi: 10.1093/eurheartj/ehz425. Erratum in: Eur Heart J. 2020 Nov 21;41(44):4242. doi: 10.1093/eurheartj/ehz825.
7. Doenst T, Thiele H, Haasenritter J, Wahlers T, Massberg S, Haverich A. The treatment of coronary artery disease. Dtsch Arztebl Int. 2022 Oct 21;119(42):716–23. doi: 10.3238/arztebl.m2022.0277.
8. Chernykh VP, editor. Pharmaceutical encyclopedia. 3rd ed., revised and expanded. Kyiv: MORION; 2016. p. 1761.
9. Kozlov IA. Pharmacological cardiac protection: what is new? Mess Anesth Resuscit. 2019;16(2):57-66. doi: 10.21292/2078-5658-2019-16-2-57-66.
10. Kawai A, Nagatomo Y, Yukino-Iwashita M, Nakazawa R, Taruoka A, Yumita Y, et al. β1 Adrenergic receptor autoantibodies and igg subclasses: current status and unsolved issues. J Cardiov Devel Disease. 2023;10(9):390. doi: 10.3390/jcdd10090390.
11. Sinagra G, Corrà U, Contini M, Magrì D, Paolillo S, Perrone Filardi P, et al. Choosing among β-blockers in heart failure patients according to β-receptors' location and functions in the cardiopulmonary system. Pharmacol Res. 2020 Jun;156:104785. doi: 10.1016/j.phrs.2020.104785.
12. Halvorsen S, Mehilli J, Cassese S, Hall TS, Abdelhamid M, Barbato E, et al. 2022 ESC Guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery: Developed by the task force for cardiovascular assessment and management of patients undergoing non-cardiac surgery of the European Society of Cardiology (ESC) Endorsed by the European Society of Anaesthesiology and Intensive Care (ESAIC). Eur Heart J. 2022;43(39):3826-924. doi: 10.1093/eurheartj/ehac270.
13. Padhani ZA, Gangwani MK, Sadaf A, Hasan B, Colan S, Alvi N, et al. Calcium channel blockers for preventing cardiomyopathy due to iron overload in people with transfusion-dependent beta thalassaemia. Cochrane Database Syst Rev. 2023 Nov 17;11(11):CD011626. doi: 10.1002/14651858.CD011626.pub3.
14. Jæger KH, Charwat V, Wall S, Healy KE, Tveito A. Do calcium channel blockers applied to cardiomyocytes cause increased channel expression resulting in reduced efficacy? NPJ Syst Biol Appl. 2024 Mar 1;10(1):22. doi: 10.1038/s41540-024-00347-3.
15. Bhullar SK, Dhalla NS. Angiotensin II-induced signal transduction mechanisms for cardiac hypertrophy. Cells. 2022 Oct 22;11(21):3336. doi: 10.3390/cells11213336.
16. Wong CK, Lau YM, Lai WH, Zhang RR, Luk HK, Wong AC, et al. Angiotensin converting enzyme and sodium glucose cotransporter inhibitors alleviate inflammatory effects of SARS-CoV-2 in cardiomyocytes. Cardiol J. 2022;29(4):702-6. doi: 10.5603/CJ.a2022.0033.
17. Zhang L, Zhang B, Yu Y, Wang J, Wu J, Su Y, et al J. Angiotensin II increases HMGB1 expression in the myocardium through AT1 and AT2 receptors when under pressure overload. Int Heart J. 2021 Jan 30;62(1):162-70. doi: 10.1536/ihj.20-384.
18. Reis T, Ronco F, Ostermann M. Diuretics and ultrafiltration in heart failure. Cardiorenal Med. 2023;13(1):56-65. doi: 10.1159/000529068..

19. Tomasoni D, Vishram-Nielsen JKK, Pagnesi M, Adamo M, Lombardi CM, Gustafsson F, et al. Advanced heart failure: guideline-directed medical therapy, diuretics, inotropes and palliative care. ESC Heart Fail. 2022 Jun;9(3):1507-23. doi: 10.1002/ehf2.13859.
20. Kim HJ, Jo SH, Lee MH, Seo WW, Kim HL, Lee KY, et al. Nitrates vs. other types of vasodilators and clinical outcomes in patients with vasospastic angina: a propensity score-matched analysis. J Clin Med. 2022 Jun 7;11(12):3250. doi: 10.3390/jcm11123250.
21. Zhu D, Hou J, Qian M, Jin D, Hao T, Pan Y, et al. Nitrate-functionalized patch confers cardioprotection and improves heart repair after myocardial infarction via local nitric oxide delivery. Nat Commun. 2021 Jul 23;12(1):4501. doi: 10.1038/s41467-021-24804-3.
22. Lionetti V, Barile L. Perioperative cardioprotection: back to bedside. Minerva Anestesiol. 2020 Apr;86(4):445-54. doi: 10.23736/S0375-9393.19.13848-5.
23. Papadopoulou A, Dickinson M, Samuels TL, Heiss C, Forni L, Creagh-Brown B. Efficacy of remote ischaemic preconditioning on outcomes following non-cardiac non-vascular surgery: a systematic review and meta-analysis. Perioper Med (Lond). 2023 Apr 10;12(1):9. doi: 10.1186/s13741-023-00297-0.
24. Momeni M, De Hert S. New advances in perioperative cardioprotection. F1000Res. 2019 Apr 24;8:F1000 Faculty Rev-538. doi: 10.12688/f1000research.17184.1.
25. Leung MK, Irwin MG. Perioperative cardioprotection. F1000Prime Rep. 2013;5:7. doi: 10.12703/P5-7.
26. Torregroza C, Roth S, Feige K, Lurati Buse G, Hollmann MW, Huhn R. Perioperative cardioprotection - From bench to bedside: Current experimental evidence and possible reasons for the limited translation into the clinical setting. Anaesthesist. 2021 May;70(5):401-412. German. doi: 10.1007/s00101-020-00912-5.
27. Guerrero-Orriach JL, Carmona-Luque MD, Gonzalez-Alvarez L. Heart failure after cardiac surgery: the role of halogenated agents, myocardial conditioning and oxidative stress. Int J Mol Sci. 2022 Jan 25;23(3):1360. doi: 10.3390/ijms23031360.
28. Piriou V, Ross S, Pigott D, Evans R, Foex P. Beneficial effect of concomitant administration of isoflurane and nicorandil. Br J Anaesth. 1997 Jul;79(1):68-77. doi: 10.1093/bja/79.1.68.
29. Wang Z, Yao M, Jiang L, Wang L, Yang Y, Wang Q, et al. Dexmedetomidine attenuates myocardial ischaemia/reperfusion-induced ferroptosis via AMPK/GSK-3β/Nrf2 axis. Biomed Pharmacother. 2022 Oct;154:113572. doi: 10.1016/j.biopha.2022.113572.
30. She H, Hu Y, Zhao G, Du Y, Wu Y, Chen W, et al. Dexmedetomidine ameliorates myocardial ischemia-reperfusion injury by inhibiting MDH2 lactylation via regulating metabolic reprogramming. Adv Sci (Weinh). 2024 Dec;11(48):e2409499. doi: 10.1002/advs.202409499.
31. Cai S, Liu Y, Cheng Y, Yuan J, Fang J. Dexmedetomidine protects cardiomyocytes against hypoxia/reoxygenation injury via multiple mechanisms. J Clin Lab Anal. 2022 Jul;36(7):e24119. doi: 10.1002/jcla.24119.
32. Caricati-Neto A, Errante PR, Menezes-Rodrigues FS. Recent advances in pharmacological and non-pharmacological strategies of cardioprotection. Int J Mol Sci. 2019 Aug 16;20(16):4002. doi: 10.3390/ijms20164002.
33. Jovanović A. Cardioprotective signalling: Past, present and future. Eur J Pharmacol. 2018 Aug 15;833:314-9. doi: 10.1016/j.ejphar.2018.06.029.
34. Penna C, Mancardi D, Rastaldo R, Pagliaro P. Cardioprotection: a radical view Free radicals in pre and postconditioning. Biochim Biophys Acta. 2009 Jul;1787(7):781-93. doi: 10.1016/j.bbabio.2009.02.008.
35. Comità S, Rubeo C, Giordano M, Penna C, Pagliaro P. Pathways for cardioprotection in perspective: focus on remote conditioning and extracellular vesicles. Biology (Basel). 2023 Feb 14;12(2):308. doi: 10.3390/biology12020308.
36. Davidson SM, Yellon DM. Exosomes and cardioprotection - A critical analysis. Mol Aspects Med. 2018 Apr;60:104-14. doi: 10.1016/j.mam.2017.11.004.
37. Madonna R, Van Laake LW, Davidson SM, Engel FB, Hausenloy DJ, Lecour S, et al. Position Paper of the European Society of Cardiology Working Group Cellular Biology of the Heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. Eur Heart J. 2016 Jun 14;37(23):1789-98. doi: 10.1093/eurheartj/ehw113.
38. Schächinger V, Erbs S, Elsässer A, Haberbosch W, Hambrecht R, Hölschermann H, et al; REPAIR-AMI Investigators. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. Eur Heart J. 2006 Dec;27(23):2775-83. doi: 10.1093/eurheartj/ehl388.
39. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet. 2004 Jul 10-16;364(9429):141-8. doi: 10.1016/S0140-6736(04)16626-9.
40. Lunde K, Solheim S, Aakhus S, Arnesen H, Abdelnoor M, Egeland T, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. N Engl J Med. 2006 Sep 21;355(12):1199-209. doi: 10.1056/NEJMoa055706.
41. Meyer GP, Wollert KC, Lotz J, Steffens J, Lippolt P, Fichtner S, et al. Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. Circulation. 2006 Mar 14;113(10):1287-94. doi: 10.1161/CIRCULATIONAHA.105.575118.
42. Huikuri HV, Kervinen K, Niemelä M, Ylitalo K, Säily M, Koistinen P, et al; FINCELL Investigators. Effects of intracoronary injection of mononuclear bone marrow cells on left ventricular function, arrhythmia risk profile, and restenosis after thrombolytic therapy of acute myocardial infarction. Eur Heart J. 2008 Nov;29(22):2723-32. doi: 10.1093/eurheartj/ehn436.
43. Estrin SI, Kravchenko TV, Gramatyuk SM, Ivanova YV, Krivoruchko IA, Minukhin DV. Cellular cardiomyoplasty in refractory angina: experimental substantiation of the optimal method and clinical experience. Ukr J Clin Surg. 2025;92(3):34-44 doi: 10.26779/2786-832X.2025.3.34.
44. Attar A, Bahmanzadegan Jahromi F, Kavousi S, Monabati A, Kazemi A. Mesenchymal stem cell transplantation after acute myocardial infarction: a meta-analysis of clinical trials. Stem Cell Res Ther. 2021 Dec 7;12(1):600. doi: 10.1186/s13287-021-02667-1.
45. Hosseinpour A, Kheshti F, Kazemi A, Attar A. Comparing the effect of bone marrow mono-nuclear cells with mesenchymal stem cells after acute myocardial infarction on improvement of left ventricular function: a meta-analysis of clinical trials. Stem Cell Res Ther. 2022 May 16;13(1):203. doi: 10.1186/s13287-022-02883-3.
46. Wöhrle J, Merkle N, Mailänder V, Nusser T, Schauwecker P, von Scheidt F, et al. Results of intracoronary stem cell therapy after acute myocardial infarction. Am J Cardiol. 2010 Mar 15;105(6):804-12. doi: 10.1016/j.amjcard.2009.10.060.

47. Zhang S, Sun A, Xu D, Yao K, Huang Z, Jin H, et al. Impact of timing on efficacy and safety of intracoronary autologous bone marrow stem cells transplantation in acute myocardial infarction: a pooled subgroup analysis of randomized controlled trials. Clin Cardiol. 2009 Aug;32(8):458-66. doi: 10.1002/clc.20575.
48. Yao K, Huang RC, Ge L, Qian JY, Li YL, Xu SK, et al. [Observation on the safety: clinical trial on intracoronary autologous bone marrow mononuclear cells transplantation for acute myocardial infarction]. Zhonghua Xin Xue Guan Bing Za Zhi. 2006 Jul;34(7):577-81. Chinese. PMID: 17081355.
49. Traverse JH, Henry TD, Ellis SG, Pepine CJ, Willerson JT, Zhao DX, et al; Cardiovascular Cell Therapy Research Network. Effect of intracoronary delivery of autologous bone marrow mononuclear cells 2 to 3 weeks following acute myocardial infarction on left ventricular function: the LateTIME randomized trial. JAMA. 2011 Nov 16;306(19):2110-9. doi: 10.1001/jama.2011.1670.
50. Perin EC, Silva GV, Henry TD, Cabreira-Hansen MG, Moore WH, Coulter SA, et al. A randomized study of transendocardial injection of autologous bone marrow mononuclear cells and cell function analysis in ischemic heart failure (FOCUS-HF). Am Heart J. 2011 Jun;161(6):1078-87.e3. doi: 10.1016/j.ahj.2011.01.028.
51. Carbone RG, Negrini S, Murdaca G, Fontana V, Puppo F. Stem cells treatment in chronic ischemic heart disease: a narrative review. Am J Stem Cells. 2023 Oct 20;12(4):65-72. PMID: 38021453.
52. Taljaard M, Ward MR, Kutryk MJ, Courtman DW, Camack NJ, Goodman SG, et al. Rationale and design of Enhanced Angiogenic Cell Therapy in Acute Myocardial Infarction (ENACT-AMI): the first randomized placebo-controlled trial of enhanced progenitor cell therapy for acute myocardial infarction. Am Heart J. 2010 Mar;159(3):354-60. doi: 10.1016/j.ahj.2009.12.021.
53. Perin EC, Sanz-Ruiz R, Sánchez PL, Lasso J, Pérez-Cano R, Alonso-Farto JC, et al. Adipose-derived regenerative cells in patients with ischemic cardiomyopathy: The PRECISE Trial. Am Heart J. 2014 Jul;168(1):88-95.e2. doi: 10.1016/j.ahj.2014.03.022.
54. Hierlihy AM, Seale P, Lobe CG, Rudnicki MA, Megeney LA. The post-natal heart contains a myocardial stem cell population. FEBS Lett. 2002 Oct 23;530(1-3):239-43. doi: 10.1016/s0014-5793(02)03477-4.
55. Martin CM, Meeson AP, Robertson SM, Hawke TJ, Richardson JA, Bates S, et al. Persistent expression of the ATP-binding cassette transporter, Abcg2, identifies cardiac SP cells in the developing and adult heart. Dev Biol. 2004 Jan 1;265(1):262-75. doi: 10.1016/j.ydbio.2003.09.028.
56. Pfister O, Mouquet F, Jain M, Summer R, Helmes M, Fine A, et al. CD31- but Not CD31+ cardiac side population cells exhibit functional cardiomyogenic differentiation. Circ Res. 2005 Jul 8;97(1):52-61. doi: 10.1161/01.RES.0000173297.53793.fa.
57. Streef TJ, Smits AM. Epicardial contribution to the developing and injured heart: exploring the cellular composition of the epicardium. Front Cardiovasc Med. 2021 Sep 23;8:750243. doi: 10.3389/fcvm.2021.750243.
58. Smart N, Bollini S, Dubé KN, Vieira JM, Zhou B, Davidson S, et al. De novo cardiomyocytes from within the activated adult heart after injury. Nature. 2011 Jun 8;474(7353):640-4. doi: 10.1038/nature10188.
59. Zhou B, Honor LB, Ma Q, Oh JH, Lin RZ, Melero-Martin JM, et al. Thymosin beta 4 treatment after myocardial infarction does not reprogram epicardial cells into cardiomyocytes. J Mol Cell Cardiol. 2012 Jan;52(1):43-7. doi: 10.1016/j.yjmcc.2011.08.020.
60. Bollini S, Vieira JM, Howard S, Dubè KN, Balmer GM, Smart N, et al. Re-activated adult epicardial progenitor cells are a heterogeneous population molecularly distinct from their embryonic counterparts. Stem Cells Dev. 2014 Aug 1;23(15):1719-30. doi: 10.1089/scd.2014.0019.
61. Cai CL, Liang X, Shi Y, Chu PH, Pfaff SL, Chen J, et al. Isl1 identifies a cardiac progenitor population that proliferates prior to differentiation and contributes a majority of cells to the heart. Dev Cell. 2003 Dec;5(6):877-89. doi: 10.1016/s1534-5807(03)00363-0.
62. Moretti A, Caron L, Nakano A, Lam JT, Bernshausen A, Chen Y, et al. Multipotent embryonic isl1+ progenitor cells lead to cardiac, smooth muscle, and endothelial cell diversification. Cell. 2006 Dec 15;127(6):1151-65. doi: 10.1016/j.cell.2006.10.029.
63. Laugwitz KL, Moretti A, Lam J, Gruber P, Chen Y, Woodard S, et al. Postnatal isl1+ cardioblasts enter fully differentiated cardiomyocyte lineages. Nature. 2005 Feb 10;433(7026):647-53. doi: 10.1038/nature03215.
64. Messina E, De Angelis L, Frati G, Morrone S, Chimenti S, Fiordaliso F, et al. Isolation and expansion of adult cardiac stem cells from human and murine heart. Circ Res. 2004 Oct 29;95(9):911-21. doi: 10.1161/01.RES.0000147315.71699.51.
65. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, Chimenti S, et al. Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell. 2003 Sep 19;114(6):763-76. doi: 10.1016/s0092-8674(03)00687-1.
66. Zaruba MM, Soonpaa M, Reuter S, Field LJ. Cardiomyogenic potential of C-kit(+)-expressing cells derived from neonatal and adult mouse hearts. Circulation. 2010 May 11;121(18):1992-2000. doi: 10.1161/CIRCULATIONAHA.109.909093.
67. Jesty SA, Steffey MA, Lee FK, Breitbach M, Hesse M, Reining S, et al. c-kit+ precursors support postinfarction myogenesis in the neonatal, but not adult, heart. Proc Natl Acad Sci U S A. 2012 Aug 14;109(33):13380-5. doi: 10.1073/pnas.1208114109.
68. Berlo JH, Kanisicak O, Maillet M, Vagnozzi RJ, Karch J, Lin SC, et al. c-kit+ cells minimally contribute cardiomyocytes to the heart. Nature. 2014 Jul 9;509(7500):337-41. doi: 10.1038/nature13309.
69. Goumans MJ, de Boer TP, Smits AM, van Laake LW, van Vliet P, Metz CH, et al. TGF-beta1 induces efficient differentiation of human cardiomyocyte progenitor cells into functional cardiomyocytes in vitro. Stem Cell Res. 2007 Nov;1(2):138-49. doi: 10.1016/j.scr.2008.02.003.
70. Oh H, Chi X, Bradfute SB, Mishina Y, Pocius J, Michael LH, et al. Cardiac muscle plasticity in adult and embryo by heart-derived progenitor cells. Ann N Y Acad Sci. 2004 May;1015:182-9. doi: 10.1196/annals.1302.015.
71. Leung HW, Moerkamp AT, Padmanabhan J, Ng SW, Goumans MJ, Choo A. mAb C19 targets a novel surface marker for the isolation of human cardiac progenitor cells from human heart tissue and differentiated hESCs. J Mol Cell Cardiol. 2015 May;82:228-37. doi: 10.1016/j.yjmcc.2015.02.016.
72. Chong JJ, Yang X, Don CW, Minami E, Liu YW, Weyers JJ, et al. Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts. Nature. 2014 Jun 12;510(7504):273-7. doi: 10.1038/nature13233.
73. Mauritz C, Schwanke K, Reppel M, Neef S, Katsirntaki K, Maier LS, et al. Generation of functional murine cardiac myocytes from induced pluripotent stem cells. Circulation. 2008 Jul 29;118(5):507-17. doi: 10.1161/CIRCULATIONAHA.108.778795.

74. Narazaki G, Uosaki H, Teranishi M, Okita K, Kim B, Matsuoka S, et al. Directed and systematic differentiation of cardiovascular cells from mouse induced pluripotent stem cells. Circulation. 2008 Jul 29;118(5):498-506. doi: 10.1161/CIRCULATIONAHA.108.769562.
75. Kawamura M, Miyagawa S, Miki K, Saito A, Fukushima S, Higuchi T, et al. Feasibility, safety, and therapeutic efficacy of human induced pluripotent stem cell-derived cardiomyocyte sheets in a porcine ischemic cardiomyopathy model. Circulation. 2012 Sep 11;126(11 Suppl 1):S29-37. doi: 10.1161/CIRCULATIONAHA.111.084343.
76. Kattman SJ, Witty AD, Gagliardi M, Dubois NC, Niapour M, Hotta A, et al. Stage-specific optimization of activin/nodal and BMP signaling promotes cardiac differentiation of mouse and human pluripotent stem cell lines. Cell Stem Cell. 2011 Feb 4;8(2):228-40. doi: 10.1016/j.stem.2010.12.008.
77. Templin C, Kotlarz D, Marquart F, Faulhaber J, Brendecke V, Schaefer A, et al. Transcoronary delivery of bone marrow cells to the infarcted murine myocardium: feasibility, cellular kinetics, and improvement in cardiac function. Basic Res Cardiol. 2006 Jul;101(4):301-10. doi: 10.1007/s00395-006-0590-7.
78. Hofmann M, Wollert KC, Meyer GP, Menke A, Arseniev L, Hertenstein B, et al. Monitoring of bone marrow cell homing into the infarcted human myocardium. Circulation. 2005 May 3;111(17):2198-202. doi: 10.1161/01.CIR.0000163546.27639.AA.
79. Blocklet D, Toungouz M, Berkenboom G, Lambermont M, Unger P, Preumont N, et al. Myocardial homing of nonmobilized peripheral-blood CD34+ cells after intracoronary injection. Stem Cells. 2006 Feb;24(2):333-6. doi: 10.1634/stemcells.2005-0201.
80. Hou D, Youssef EA, Brinton TJ, Zhang P, Rogers P, Price ET, et al. Radiolabeled cell distribution after intramyocardial, intracoronary, and interstitial retrograde coronary venous delivery: implications for current clinical trials. Circulation. 2005 Aug 30;112(9 Suppl):I150-6. doi: 10.1161/CIRCULATIONAHA.104.526749.
81. Karbassi E, Fenix A, Marchiano S, Muraoka N, Nakamura K, Yang X, et al. Cardiomyocyte maturation: advances in knowledge and implications for regenerative medicine. Nat Rev Cardiol. 2020 Jun;17(6):341-59. doi: 10.1038/s41569-019-0331-x.
82. Smart N, Riley PR. The stem cell movement. Circ Res. 2008 May 23;102(10):1155-68. doi: 10.1161/CIRCRESAHA.108.175158.
83. Pijnappels DA, Gregoire S, Wu SM. The integrative aspects of cardiac physiology and their implications for cell-based therapy. Ann N Y Acad Sci. 2010 Feb;1188:7-14. doi: 10.1111/j.1749-6632.2009.05077.x.
84. Afzal MR, Samanta A, Shah ZI, Jeevanantham V, Abdel-Latif A, Zuba-Surma EK, et al. Adult bone marrow cell therapy for ischemic heart disease: evidence and insights from randomized controlled trials. Circ Res. 2015 Aug 28;117(6):558-75. doi: 10.1161/CIRCRESAHA.114.304792.
85. Lecour S, Bøtker HE, Condorelli G, Davidson SM, Garcia-Dorado D, Engel FB, et al. ESC working group cellular biology of the heart: position paper: improving the preclinical assessment of novel cardioprotective therapies. Cardiovasc Res. 2014 Dec 1;104(3):399-411. doi: 10.1093/cvr/cvu225.
86. Davidson SM, Takov K, Yellon DM. Exosomes and cardiovascular protection. Cardiovasc Drugs Ther. 2017 Feb;31(1):77-86. doi: 10.1007/s10557-016-6698-6.
87. Arroyo-Campuzano M, Zazueta C. [Significance of exosomes in cardiology: heralds of cardioprotection]. Arch Cardiol Mex. 2021;91(1):105-13. Spanish. doi: 10.24875/ACM.20000335.
88. Rezaie J, Rahbarghazi R, Pezeshki M, Mazhar M, Yekani F, Khaksar M, et al. Cardioprotective role of extracellular vesicles: A highlight on exosome beneficial effects in cardiovascular diseases. J Cell Physiol. 2019 Dec;234(12):21732-45. doi: 10.1002/jcp.28894.
89. Trams EG, Lauter CJ, Salem N Jr, Heine U. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles. Biochim Biophys Acta. 1981 Jul 6;645(1):63-70. doi: 10.1016/0005-2736(81)90512-5.
90. Pan BT, Teng K, Wu C, Adam M, Johnstone RM. Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. J Cell Biol. 1985 Sep;101(3):942-8. doi: 10.1083/jcb.101.3.942.
91. Jadli AS, Parasor A, Gomes KP, Shandilya R, Patel VB. Exosomes in cardiovascular diseases: pathological potential of nano-messenger. Front Cardiovasc Med. 2021 Nov 12;8:767488. doi: 10.3389/fcvm.2021.767488.
92. Comfort N, Cai K, Bloomquist TR, Strait MD, Ferrante AW Jr, Baccarelli AA. Nanoparticle tracking analysis for the quantification and size determination of extracellular vesicles. J Vis Exp. 2021 Mar 28;(169):10.3791/62447. doi: 10.3791/62447.
93. Li D, Zhao Y, Zhang C, Wang F, Zhou Y, Jin S. Plasma exosomes at the late phase of remote ischemic pre-conditioning attenuate myocardial ischemia-reperfusion injury through transferring miR-126a-3p. Front Cardiovasc Med. 2021 Nov 30;8:736226. doi: 10.3389/fcvm.2021.736226.
94. Kowal J, Arras G, Colombo M, Jouve M, Morath JP, Primdal-Bengtson B, et al. Proteomic comparison defines novel markers to characterize heterogeneous populations of extracellular vesicle subtypes. Proc Natl Acad Sci U S A. 2016 Feb 23;113(8):E968-77. doi: 10.1073/pnas.1521230113.
95. Haraszti RA, Didiot MC, Sapp E, Leszyk J, Shaffer SA, Rockwell HE, et al. High-resolution proteomic and lipidomic analysis of exosomes and microvesicles from different cell sources. J Extracell Vesicles. 2016 Nov 17;5:32570. doi: 10.3402/jev.v5.32570.
96. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. Cell Biosci. 2019 Feb 15;9:19. doi: 10.1186/s13578-019-0282-2.
97. Théry C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. Nat Rev Immunol. 2002 Aug;2(8):569-79. doi: 10.1038/nri855.
98. Mathivanan S, Ji H, Simpson RJ. Exosomes: extracellular organelles important in intercellular communication. J Proteomics. 2010 Sep 10;73(10):1907-20. doi: 10.1016/j.jprot.2010.06.006.
99. Reddy VS, Madala SK, Trinath J, Reddy GB. Extracellular small heat shock proteins: exosomal biogenesis and function. Cell Stress Chaperones. 2018 May;23(3):441-54. doi: 10.1007/s12192-017-0856-z.
100. Göran Ronquist K. Extracellular vesicles and energy metabolism. Clin Chim Acta. 2019 Jan;488:116-21. doi: 10.1016/j.cca.2018.10.044.
101. Inubushi S, Kunihisa T, Kuniyasu M, Inoue S, Yamamoto M, Yamashita Y, et al. Serum exosomes expressing CD9, CD63 and HER2 from breast-cancer patients decreased after surgery of the primary tumor: a potential biomarker of tumor burden. Cancer Genomics Proteomics. 2024 Nov-Dec;21(6):580-4. doi: 10.21873/cgp.20474.
102. Isaac R, Reis FCG, Ying W, Olefsky JM. Exosomes as mediators of intercellular crosstalk in metabolism. Cell Metab. 2021 Sep 7;33(9):1744-62. doi: 10.1016/j.cmet.2021.08.006.
103. Elsherbini A, Bieberich E. Ceramide and exosomes: a novel target in cancer biology and therapy. Adv Cancer Res. 2018;140:121-154. doi: 10.1016/bs.acr.2018.05.004.
104. Peppicelli S, Calorini L, Bianchini F, Papucci L, Magnelli

L, Andreucci E. Acidity and hypoxia of tumor microenvironment, a positive interplay in extracellular vesicle release by tumor cells. Cell Oncol (Dordr). 2025 Feb;48(1):27-41. doi: 10.1007/s13402-024-00969-z.
105. Yuyama K, Yamamoto N, Yanagisawa K. Accelerated release of exosome-associated GM1 ganglioside (GM1) by endocytic pathway abnormality: another putative pathway for GM1-induced amyloid fibril formation. J Neurochem. 2008 Apr;105(1):217-24. doi: 10.1111/j.1471-4159.2007.05128.x.
106. Subra C, Grand D, Laulagnier K, Stella A, Lambeau G, Paillasse M, et al. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. J Lipid Res. 2010 Aug;51(8):2105-20. doi: 10.1194/jlr.M003657.
107. Kalluri R, LeBleu VS. Discovery of double-stranded genomic DNA in circulating exosomes. Cold Spring Harb Symp Quant Biol. 2016;81:275-80. doi: 10.1101/sqb.2016.81.030932.
108. Mallat Z, Benamer H, Hugel B, Benessiano J, Steg PG, Freyssinet JM, et al. Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. Circulation. 2000 Feb 29;101(8):841-3. doi: 10.1161/01.cir.101.8.841.
109. Zhang J. Biomarkers of endothelial activation and dysfunction in cardiovascular diseases. Rev Cardiovasc Med. 2022 Feb 22;23(2):73. doi: 10.31083/j.rcm2302073.
110. Martinez MC, Andriantsitohaina R. Microparticles in angiogenesis: therapeutic potential. Circ Res. 2011 Jun 24;109(1):110-9. doi: 10.1161/CIRCRESAHA.110.233049.
111. Kim HK, Song KS, Chung JH, Lee KR, Lee SN. Platelet microparticles induce angiogenesis in vitro. Br J Haematol. 2004 Feb;124(3):376-84. doi: 10.1046/j.1365-2141.2003.04773.x.
112. Brill A, Dashevsky O, Rivo J, Gozal Y, Varon D. Platelet-derived microparticles induce angiogenesis and stimulate post-ischemic revascularization. Cardiovasc Res. 2005 Jul 1;67(1):30-8. doi: 10.1016/j.cardiores.2005.04.007.
113. Heijnen HF, Schiel AE, Fijnheer R, Geuze HJ, Sixma JJ. Activated platelets release two types of membrane vesicles: microvesicles by surface shedding and exosomes derived from exocytosis of multivesicular bodies and alpha-granules. Blood. 1999 Dec 1;94(11):3791-9. PMID: 10572093.
114. Tang Y, Li J, Wang W, Chen B, Chen J, Shen Z, et al. Platelet extracellular vesicles enhance the proangiogenic potential of adipose-derived stem cells in vivo and in vitro. Stem Cell Res Ther. 2021 Sep 9;12(1):497. doi: 10.1186/s13287-021-02561-w.
115. Malik ZA, Kott KS, Poe AJ, Kuo T, Chen L, Ferrara KW, et al. Cardiac myocyte exosomes: stability, HSP60, and proteomics. Am J Physiol Heart Circ Physiol. 2013 Apr 1;304(7):H954-65. doi: 10.1152/ajpheart.00835.2012.
116. Krishnan-Sivadoss I, Mijares-Rojas IA, Villarreal-Leal RA, Torre-Amione G, Knowlton AA, Guerrero-Beltrán CE. Heat shock protein 60 and cardiovascular diseases: An intricate love-hate story. Med Res Rev. 2021 Jan;41(1):29-71. doi: 10.1002/med.21723.
117. Gupta S, Knowlton AA. HSP60 trafficking in adult cardiac myocytes: role of the exosomal pathway. Am J Physiol Heart Circ Physiol. 2007 Jun;292(6):H3052-6. doi: 10.1152/ajpheart.01355.2006.
118. Liu N, Xie L, Xiao P, Chen X, Kong W, Lou Q, et al. Cardiac fibroblasts secrete exosome microRNA to suppress cardiomyocyte pyroptosis in myocardial ischemia/reperfusion injury. Mol Cell Biochem. 2022 Apr;477(4):1249-60. doi: 10.1007/s11010-021-04343-7.
119. Ferrer J, Dimitrova N. Transcription regulation by long non-coding RNAs: mechanisms and disease relevance. Nat Rev Mol Cell Biol. 2024 May;25(5):396-415. doi: 10.1038/s41580-023-00694-9.
120. Marinescu MC, Lazar AL, Marta MM, Cozma A, Catana CS. Non-Coding RNAs: prevention, diagnosis, and treatment in myocardial ischemia-reperfusion injury. Int J Mol Sci. 2022 Mar 1;23(5):2728. doi: 10.3390/ijms23052728.
121. Davidson SM, Andreadou I, Barile L, Birnbaum Y, Cabrera-Fuentes HA, Cohen MV, et al. Circulating blood cells and extracellular vesicles in acute cardioprotection. Cardiovasc Res. 2019 Jun 1;115(7):1156-66. doi: 10.1093/cvr/cvy314.
122. Sun SJ, Wei R, Li F, Liao SY, Tse HF. Mesenchymal stromal cell-derived exosomes in cardiac regeneration and repair. Stem Cell Reports. 2021 Jul 13;16(7):1662-73. doi: 10.1016/j.stemcr.2021.05.003.
123. Van Delen M, Derdelinckx J, Wouters K, Nelissen I, Cools N. A systematic review and meta-analysis of clinical trials assessing safety and efficacy of human extracellular vesicle-based therapy. J Extracell Vesicles. 2024 Jul;13(7):e12458. doi: 10.1002/jev2.12458.
124. Barile L, Marbán E. Injury minimization after myocardial infarction: focus on extracellular vesicles. Eur Heart J. 2024 May 13;45(18):1602-1609. doi: 10.1093/eurheartj/ehae089.
125. Barungi S, Hernández-Camarero P, Moreno-Terribas G, Villalba-Montoro R, Marchal JA, López-Ruiz E, et al. Clinical implications of inflammation in atheroma formation and novel therapies in cardiovascular diseases. Front Cell Dev Biol. 2023 Mar 16;11:1148768. doi: 10.3389/fcell.2023.1148768.
126. Rayat Pisheh H, Sani M. Mesenchymal stem cells derived exosomes: a new era in cardiac regeneration. Stem Cell Res Ther. 2025 Jan 23;16(1):16. doi: 10.1186/s13287-024-04123-2.
127. Zhang N, Luo Y, Zhang H, Zhang F, Gao X, Shao J. Exosomes derived from mesenchymal stem cells ameliorate the progression of atherosclerosis in ApoE-/- Mice via FENDRR. Cardiovasc Toxicol. 2022 Jun;22(6):528-44. doi: 10.1007/s12012-022-09736-8.
128. Ma J, Chen L, Zhu X, Li Q, Hu L, Li H. Mesenchymal stem cell-derived exosomal miR-21a-5p promotes M2 macrophage polarization and reduces macrophage infiltration to attenuate atherosclerosis. Acta Biochim Biophys Sin (Shanghai). 2021 Aug 31;53(9):1227-36. doi: 10.1093/abbs/gmab102.
129. Sapna F, Raveena F, Chandio M, Bai K, Sayyar M, Varrassi G, et al. Advancements in heart failure management: a comprehensive narrative review of emerging therapies. Cureus. 2023 Oct 4;15(10):e46486. doi: 10.7759/cureus.46486.
130. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. Science. 2017 Jun 9;356(6342):1026-30. doi: 10.1126/science.aam7928.
131. Yan F, Cui W, Chen Z. Mesenchymal stem cell-derived exosome-loaded microRNA-129-5p inhibits TRAF3 expression to alleviate apoptosis and oxidative stress in heart failure. Cardiovasc Toxicol. 2022 Jul;22(7):631-45. doi: 10.1007/s12012-022-09743-9.
132. Ke X, Yang R, Wu F, Wang X, Liang J, Hu X, et al. Exosomal miR-218-5p/miR-363-3p from endothelial progenitor cells ameliorate myocardial infarction by targeting the p53/jmy signaling pathway. Oxid Med Cell Longev. 2021 Jul 16;2021:5529430. doi: 10.1155/2021/5529430.