

Mini Review

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# Cardiac Regeneration Innovation in the Clinical Trial Pipeline

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## Article Info

### Article Notes

Received: September 16, 2025  
Accepted: October 14, 2025

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### Keywords

Cardiac regeneration  
Heart failure  
Myocardial infarction  
Stem cell therapy  
Autologous cells  
Allogeneic cells  
Gene therapy  
Clinical trials

## Abstract

Cardiovascular diseases remain the leading cause of mortality worldwide, with limited capacity for myocardial regeneration following injury. Regenerative strategies, including autologous and allogeneic cell-based therapies, gene therapy, and tissue constructs, are being investigated as potential approaches to restore cardiac function. We searched ClinicalTrials.gov on August 16, 2025, using the terms “heart regeneration”, restricting to interventional trials in phases 1-3. Trials unrelated to cardiac regeneration were excluded. Study characteristics were analyzed by condition, intervention type, phase, geographic distribution, sponsor, age group, and enrollment size. For completed studies, associated publications were reviewed to summarize efficacy and safety outcomes. Of 41 identified trials, 23 met inclusion criteria. Most were early-phase studies (11 phase 1, 9 phase 2, 3 phase 3). Myocardial infarction was the most common target (9 trials), followed by heart failure (8), coronary artery disease (5), and congenital heart disease (1). Autologous strategies predominated, though several allogeneic stem cell and gene therapy trials were also represented. The United States (6 trials) and Spain (5) were the leading contributors, followed by Germany (3), the Republic of Korea (3), and Poland (2). Enrollment ranged from 6 to 420 participants. Publications from completed trials demonstrated consistent safety but variable efficacy in improving left ventricular function and infarct size. Clinical research into cardiac regeneration remains dominated by small, early-phase, investigator-led studies, with limited large-scale, industry-driven development. While feasibility and safety have been established, efficacy signals remain inconsistent, underscoring the need for larger trials to clarify therapeutic benefit.

## Introduction

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide, accounting for an estimated 19.8 million deaths annually<sup>1</sup>. Despite advances in pharmacological therapy, device-based interventions, and surgical procedures, current treatments largely address symptoms and disease progression rather than repairing damaged myocardium<sup>2</sup>. Myocardial infarction and chronic heart failure, in particular, are characterized by irreversible loss of cardiomyocytes and maladaptive remodeling, underscoring the urgent need for regenerative approaches that can restore cardiac structure and function<sup>3</sup>. In this study, we analyze interventional trials registered on ClinicalTrials.gov that focus on regenerative strategies for heart repair, with particular emphasis on trial phase, intervention type, targeted condition, funding source, and geographic distribution.

## Materials and Methods

Clinical trial data were downloaded from ClinicalTrials.gov on August 16, 2025, using the following search criteria:

- Other terms: Heart Regeneration

- Study Type: Interventional
- Study Phase: Early phase 1, phase 1, phase 2, phase 3

The final query string combined these components: (Heart Regeneration) AND interventional AND (Early Phase 1 OR Phase 1 OR Phase 2 OR Phase 3).

As of August 16, 2025, we identified 50 interventional clinical trials that met our search criteria. Inclusion criteria were interventional trials investigating regenerative approaches targeting cardiovascular conditions. Nine trials were removed because their status was “Terminated” or “Withdrawn”. Additionally, 18 trials were excluded for reasons unrelated to cardiac regeneration (non-cardiac regeneration, non-regenerative interventions, or unrelated conditions).

In our analysis, trials designated as “Early phase 1” were grouped with phase 1 trials. “Phase 1/phase 2” trials were also combined with phase 1 trials, while “phase 2/phase 3” trials were merged with Phase 2 trials.

Study details for each clinical trial were analyzed. Cardiovascular conditions were grouped according to disease category. The categories applied to the analysis are:

- Myocardial Infarction - Acute Myocardial Infarction, Old Myocardial Infarction, Acute Coronary Syndrome
- Heart Failure - Acute Myocardial Infarction Induced Heart Failure, Left Ventricular Dysfunction, Chronic Heart Failure, Heart Failure with Reduced Ejection Fraction, Congestive Heart Failure, Dilated Cardiomyopathy, Congestive Heart Failure Patients Post Myocardial Infarction, Ischemic Cardiomyopathy
- Congenital Heart Disease - Tetralogy of Fallot, Double Outlet Right Ventricle
- Coronary Artery Disease - Coronary Disease, Angina, Coronary Heart Disease, Coronary Arteriosclerosis, Chronic Myocardial Ischemia, Coronary Atherosclerosis

For the purposes of this study, the categories ADULT and OLDER\_ADULT were combined and analyzed as a single group, hereafter referred to as Adult.

For trials classified as “Completed,” publications associated with their respective NCT numbers were reviewed to extract details on safety and efficacy outcomes.

This methodological approach followed the same principles as described previously for landscape analyses of ClinicalTrials.gov datasets<sup>4,5</sup>.

## Results

As of August 16, 2025, a total of 23 trials on ClinicalTrials.gov met our selection criteria. Of these, 14 trials were

reported as completed, 3 are currently recruiting, and 6 had an unknown or not reported status. Most trials were early phase studies: 11 Phase 1, 9 Phase 2, and 3 Phase 3. Characteristics of these trials are summarized in Table 1. This dataset does not represent a complete list of trials during this period, as some clinical studies may not be registered on ClinicalTrials.gov.

As of August 16, 2025, interventions for cardiac repair include a diverse range of approaches. Autologous strategies are the most represented, comprising skeletal myoblasts (MyoCell), c-kit positive cardiac stem cells, cardiac stem cells, bone marrow-derived and peripheral blood stem cells, as well as mobilization with Granulocyte Colony-Stimulating Factor (G-CSF). Allogeneic approaches include Wharton’s jelly-derived mesenchymal stem cells, umbilical cord-derived stem cells, expanded and cryopreserved allogeneic constructs (PeriCord), and allogeneic cardiac stem cells. Additional modalities are represented by gene therapy (AAV9-Sav-shRNA), surgical constructs (pericardial adipose pedicle), and pharmacological agents (propranolol).

Myocardial infarction was the most commonly studied condition, with 9 trials across phases 1-3. Heart failure followed closely, with 8 trials, while coronary artery disease accounted for 5 trials, and congenital heart disease was represented by 1 trial. Most studies enrolled adult participants (20 trials), though 2 trials included both adults and 1 trial included only children.

Endpoints across trials were highly heterogeneous, ranging from safety-focused measures (dose-limiting toxicities (DLTs), adverse events (AEs), maximum tolerated dose (MTD)) in early phases to functional, structural, and patient-centered outcomes in later studies (left ventricular ejection fraction (LVEF), left ventricular (LV) volumes, infarct size, 6-minute walk test (6MWT), New York Heart Association (NYHA) class, quality-of-life scores).

The United States and Spain hosted the most trials (6 and 5 trials, respectively), followed by Germany (3), the Republic of Korea (3), and Poland (2). Single studies were reported in Iran, Colombia, and Japan. In terms of sponsorship, academic and hospital-based investigators led the majority (17 trials, classified as “Other”), while industry sponsors accounted for 5 trials, and government-funded studies were limited to 1.

Enrollment varied widely, ranging from small pilot studies with 6-20 participants to larger controlled trials enrolling up to 420 patients. The largest study was a Phase 3 trial of umbilical cord-derived Wharton’s jelly mesenchymal stem cells in heart failure (NCT05043610, n=420, Iran). The earliest study included was a Phase 1 trial of bone marrow cells in coronary artery disease conducted in Germany between 2002 and 2003 (NCT00224536). The most recent study is an ongoing Phase 1 trial of gene

therapy YAP101 for heart failure in the United States (NCT06831825), expected to complete in 2027.

The publications associated with NCT numbers for completed clinical trials were further investigated.

**Table 1.** Registered Clinical Trials (as of August 16, 2025, ClinicalTrials.gov)

Trial ID	Therapy category	Cell/Source and Delivery Route	Phase/ Status/ Years/ Condition	Sample size	Sponsor Type/ Region	Primary and secondary endpoints	Key efficacy signal	Safety notes
NCT06831825	Gene therapy	AAV9 vector (Sav-shRNA), transcatheter cardiac injection	Ph1 Recruiting 2025-2027 Heart Failure	24	Industry United States	DLTs, AEs, MTD, 12 months; 6MWT, NYHA class, MACE, cumulative days alive/out-of-hospital, LVEF (MRI), LV volumes and indices (EDV, EDVI, ESV, ESVI, MRI), PVC and AFib burden, BNP and NT-proBNP, MLHFQ, survival, cardiac transplant, LVAD implantation, anti-AAV9 antibodies; 12 months	Unknown	Unknown
NCT06364150	Cell therapy	Autologous peripheral blood stem cells (Ang1-primed, mobilized with G-CSF/EPO), intracoronary infusion	Ph3 Recruiting 2024-2026 Myocardial Infarction	30	Government Republic of Korea	LVEF (echo), 12 months; RWMSI (echo), BNP, 6MWT, all-cause death, target/non-target lesion revascularization, readmission, CV death; 12 months.	Unknown	Unknown
NCT04713657	Small molecule	Propranolol (oral), systemic administration	Ph1 Recruiting 2022-2030 Congenital Heart Disease	40	Other United States	Cardiomyocyte division (MIMS), 3-9 months; RV hypertrophy by echo, MRI, and microscopy; 1 month and surgery	Unknown	Unknown
NCT05043610	Cell therapy	Allogeneic Wharton's Jelly-derived MSCs (umbilical cord), intracoronary infusion	Ph3 Completed 2021-2024 Heart Failure	420	Other Iran	Incidence of HF, 3 years; change in LV function (echo), CV death, composite of CV death/HF; 6 months and 3 years	Unknown	Unknown
NCT04551443	Cell therapy	Allogeneic Wharton's Jelly-derived MSCs (umbilical cord), intravenous infusion	Ph2 Unknown 2020-2022 Myocardial Infarction	200	Other Unknown	MACE, change in LVEF (MRI), infarct size, perfusion defect (MIBI SPECT), coronary events, HF, hsCRP; 6–12 months	Unknown	Unknown
NCT03798353	Biomaterial + Cell therapy	Allogeneic Wharton's Jelly-derived MSCs seeded on decellularized human pericardial matrix (PeriCord), epicardial placement during CABG via sternotomy	Ph1 Completed 2019-2022 Myocardial Infarction	12	Other Spain	Death/rehospitalization or procedure-related AE, 12 months; death/rehospitalization (CV causes), arrhythmias (Holter), NT-proBNP/hsTnI, necrotic myocardial mass, regional contractility (NMR), LVEF, LV/RV remodeling, SF-36, KCCQ; 1 week-12 months	No significant improvements were observed in secondary outcomes such as cardiac function or quality of life. However, PeriCord treatment modulated circulating monocyte dynamics, promoting a shift toward non-classical inflammation-resolving subsets and altering levels of monocyte chemoattractant and the prognostic marker Meteorin-like, suggesting an immunomodulatory role in post-infarction repair <sup>6</sup> .	Patients treated with PeriCord experienced no implant-related adverse effects during surgery or one-year follow-up, and implantation did not affect operative time or recovery <sup>6</sup> .
NCT04011059	Biomaterial + Cell therapy	Allogeneic Wharton's Jelly-derived MSCs with extracellular matrix patch, intramyocardial injection + epicardial patch placement during CABG surgery	Ph1 Unknown 2019-2023 Coronary Artery Disease	40	Other Colombia	LVEF (echo/MRI), final diastolic/systolic volumes, LV viability (MRI), ventricular arrhythmias, 12 months; NYHA class, MLHFQ, delayed enhancement (MRI), 6MWT, mortality (CV and all-cause), 12 months	Unknown	Unknown

NCT03418233	Cell therapy	Allogeneic Wharton's Jelly-derived MSCs (CardioCell), transcatheter or trans-catheter graft infusion	Ph2 Completed 2018-2021 Heart Failure	115	Other Poland	LVEF increase (SPECT), 6 months; 6MWT, myocardial perfusion (SPECT, MRI), spirometric test, LVEF change (echo), LV ESV/EDV (echo), NT-proBNP, MACE, quality of life (SF-36), 6 months-1 year	Unkown	Unkown
NCT03351400	Cell therapy	Autologous c-kit <sup>+</sup> cardiac stem cells, intracoronary infusion	Ph1 Unknown 2017-2022 Heart Failure	6	Other Japan	AEs (death, arrhythmia, bleeding, MI, stroke, embolism), 2 years; NYHA class, NT-proBNP, ECG, chest X-ray, CPET, echo, MRI, myocardial scintigraphy, 2 years	Unkown	Unkown
NCT03404063	Cell therapy	Allogeneic Wharton's Jelly-derived MSCs (CardioCell), intracoronary infusion	Ph2 Completed 2017-2021 Myocardial Infarction	105	Other Poland	Infarct size reduction (MRI, SPECT), 6 months; myocardial perfusion (SPECT, MRI), LVEF (MRI, SPECT, echo), LV volumes (ESV, EDV, echo), MACE, quality of life (SF-36), 6 months-1 year	Cardiac MRI showed a significant reduction in infarct size from 33.2 ± 7.6 g at baseline to 25.5 ± 6.4 g at 1 year and 23.1 ± 5.6 g at 3 years (p=0.03 vs. baseline). Across cardiac MRI, Single Photon Emission Computed Tomography, and echocardiography, Left Ventricular Ejection Fraction (LVEF) improved significantly at 6-12 months and the gains persisted at 3 years <sup>7</sup> .	Intracoronary delivery of Wharton's jelly-derived mesenchymal stem cells was safe, with no impairment of coronary (TIMI-3 in all cases) or myocardial perfusion (cTFC 45 ± 8 vs. 44 ± 9, p=0.51) and no procedure-related troponin rise. Over three years of follow-up, one patient experienced a fatal non-index myocardial infarction, but no other major adverse cardiovascular and cerebrovascular events or cell-related adverse events occurred <sup>7</sup> .
NCT02439398	Cell therapy	Allogeneic cardiac stem cells, intracoronary infusion	Ph1 Completed 2014-2016 Myocardial Infarction	55	Industry Spain	Deaths, MACE; 30 days-12 months; infarct size, LV biomechanical parameters (ESV, EDV, wall motion, sphericity, EF), edema (MRI), 1-12 months	No group differences were seen in MRI efficacy outcomes, with an estimated treatment effect on infarct size of -2.3% (95% CI -6.5 to 1.9) <sup>8</sup> .	Among 49 patients (33 AlloCSC-01, 16 placebo), no deaths or major adverse cardiac events occurred over 12 months. One possibly treatment-related severe adverse event was observed in each group, and low-level donor-specific antibodies developed in two AlloCSC-01 patients without clinical consequences <sup>8</sup> .
NCT01473433	Biomaterial	Autologous pericardial adipose tissue, surgical transposition	Ph1 Completed 2012-2014 Myocardial Infarction	10	Other Spain	Procedure-related AEs (7 days, 1 year); cardiac function (clinical, echo, MRI, NT-proBNP, hsTnT), 12 months	MRI follow-up showed a trend toward reduced LV end-systolic volume and necrosis ratio in the AGTP arm at 3 months, though not sustained at 12 months. One AGTP-treated patient with extensive baseline damage demonstrated marked long-term improvements in necrotic mass and ventricular volumes <sup>9</sup> .	Safety outcomes were similar between groups, with no differences in clinical or arrhythmic events <sup>7</sup> .
NCT01214499	Cell + Surgical	Autologous bone marrow stem cells, intramyocardial injection	Ph2 Unknown 2010-2012 Coronary Artery Disease	20	Other Spain	NYHA class improvement for angina, 1 year; demographics, intra/postoperative variables, SPECT ischemic area, LV volumes (echo/MRI), LVEF, quality of life (EQ-5D), 1 year	Unkown	Unkown
NCT01454323	Cell therapy	Autologous bone marrow mononuclear cells, intracoronary infusion	Ph2 Completed 2010-2015 Coronary Artery Disease	20	Other Spain	LVEF change, 3, 6, 12 months; MACE, NYHA class, 3, 6, 12 months	Unkown	Unkown
NCT00474461	Cell therapy	Autologous cardiac stem cells, intracoronary infusion	Ph1 Completed 2009-2013 Heart Failure	33	Other United States	AEs (death, VT, infection, bleeding, MI, stroke, embolism), 1.5 years	Unkown	Unkown

NCT00629096	Cell therapy	Autologous bone marrow mononuclear cells, intracoronary infusion	Ph2 Completed 2008-2010 Heart Failure	27	Other Spain	Improvement in LV function, 6, 12 months; functional status, 6, 12 months	At 6 months, mean angiographic LVEF improved by 9%, with 78% of patients showing a significant gain (average +14%) and 22% showing no response (average -5%). Responders were younger than non-responders, and greater LVEF improvement was associated with lower High-Density Lipoprotein levels ( $r = -0.41, p < 0.003$ ). Additionally, infused cells from responders demonstrated reduced migratory activity toward Vascular Endothelial Growth Factor and Stromal Cell-Derived Factor 1 compared with non-responders <sup>10</sup> .	
NCT00548613	Cell therapy	Autologous bone marrow-derived stem/progenitor cell combination, intracoronary infusion and intramyocardial injection	Ph1 Completed 2007-2009 Coronary Artery Disease	20	Industry United States	Safety, 6 months	Unkown	Unkown
NCT00501917	Cell therapy	Autologous peripheral blood stem cells mobilized with G-CSF ± darbepoetin, intracoronary infusion	Ph2 Unknown 2007-2010 Myocardial Infarction	116	Other Republic of Korea	LVEF change (MRI), wall motion score, exercise capacity, BNP, 6, 12, 24 months	Unkown	Unkown
NCT00938847	Cell therapy	Autologous bone marrow mononuclear cells, endoventricular catheter injection	Ph3 Completed 2006-2008 Heart Failure	20	Industry Germany	Safety/feasibility, LVEMM (NOGA) for myocardial regeneration, 12 months	Unkown	Unkown
NCT00669227	Cell therapy	Autologous bone marrow stem cells (Ficoll-prepared), intracoronary infusion	Ph2 Completed 2005 - Unknown	42	Other Germany	LVEF (MRI) change 6 months; LV volumes (MRI), MACE, 1, 3, 6, 12 months	Unkown	Unkown
NCT00291629	Cell therapy	Autologous peripheral blood stem cells mobilized with G-CSF, intracoronary infusion	Ph2 Completed 2004-2007 Myocardial Infarction	96	Other Republic of Korea	LVEF (MRI) change 6 months; LV volumes (echo/MRI), myocardial perfusion, MACE, 6 months	Unkown	Unkown
NCT00054678	Cell therapy	Autologous skeletal myoblasts (MyoCell™), transendocardial injection	Ph1 Unknown 2003-2007 Heart Failure	20	Industry United States	Safety	Unkown	Unkown
NCT00224536	Cell therapy	Autologous bone marrow cells, intracoronary infusion	Ph1 Completed 2002-2003 Coronary Artery Disease	60	Other Germany	LVEF change, 6 months; safety, LV volumes, infarct size, subgroup analyses	Unkown	Unkown

AE - Adverse Event, AMI - Acute Myocardial Infarction, BNP - B-type Natriuretic Peptide, CPET - Cardiopulmonary Exercise Test, CV - Cardiovascular, DLT - Dose-Limiting Toxicity, EDV - End-Diastolic Volume, EDVI - End-Diastolic Volume Index, ESV - End-Systolic Volume, ESVI - End-Systolic Volume Index, GABG - Coronary Artery Bypass Graft, G-CSF - Granulocyte Colony-Stimulating Factor, HF - Heart Failure, hsCRP - High-Sensitivity C-Reactive Protein, hsTnI - High-Sensitivity Troponin I, KCCQ - Kansas City Cardiomyopathy Questionnaire, LVEF - Left Ventricular Ejection Fraction, LVAD - Left Ventricular Assist Device, LVEMM - Left Ventricular Electromechanical Mapping, MACE - Major Adverse Cardiac Events, MIBI - Methoxyisobutylisonitrile (used in SPECT imaging), MLHF - Minnesota Living with Heart Failure Questionnaire, MRI - Magnetic Resonance Imaging, MSI - Mesenchymal stem cells, NOGA - NOGA Endocardial Mapping System, NSTV - Nonsustained Ventricular Tachycardia, NYHA - New York Heart Association Classification, PCI - Percutaneous Coronary Intervention, PVC - Premature Ventricular Contraction, RV - Right Ventricle, SPECT - Single Photon Emission Computed Tomography, VT - Ventricular Tachycardia, VF - Ventricular Fibrillation.

## Discussion

This report provides an overview of clinical trials on heart regeneration registered on ClinicalTrials.gov as of August 16, 2025. A total of 23 clinical trials were identified, with most being early-phase studies, reflecting the exploratory nature of regenerative approaches in cardiology.

Autologous stem cell strategies historically dominated the field, particularly those based on bone marrow and peripheral blood stem cells, but in recent years there has been a marked shift toward allogeneic sources, especially Wharton's jelly-derived mesenchymal stem cells and umbilical cord-derived constructs. This transition likely reflects the advantages of allogeneic products, including standardized manufacturing, off-the-shelf availability, and avoidance of patient-to-patient variability<sup>11</sup>. Beyond cell-based therapies, novel modalities are also emerging. Gene therapy approaches, exemplified by the ongoing trial of YAP101 (AAV9-Sav-shRNA) for heart failure (NCT06831825), aim to directly modulate molecular pathways involved in cardiac repair. Pharmacologic strategies, such as the use of propranolol hydrochloride in congenital heart disease (NCT04713657), represent another frontier, integrating traditional pharmacology with regenerative cardiology.

Condition-specific patterns were also observed. Myocardial infarction and heart failure together accounted for the majority of trials, consistent with the high burden of these diseases and the unmet need for therapies that address post-infarction remodeling and progressive ventricular dysfunction<sup>12</sup>. Coronary artery disease was less frequently represented, possibly due to the availability of established interventional and surgical treatments in these populations<sup>13</sup>.

Across the included trials, primary and secondary endpoints were highly heterogeneous, reflecting the exploratory nature of regenerative strategies in cardiology. Safety-related outcomes were universally prioritized in early-phase studies, underscoring the emphasis on feasibility and tolerability at this stage. In contrast, later-phase trials increasingly incorporated functional and clinical endpoints. These markers aimed to capture not only physiological improvement but also patient-centered outcomes. However, the lack of uniformity in endpoint selection and timing limits comparability across studies. For example, LVEF was variably assessed by MRI, echocardiography, or SPECT, often at different timepoints (3, 6, 12, or 24 months), which complicates pooled analyses. Some studies emphasized short-term surrogate markers (cardiomyocyte division, perfusion indices or monocyte profiles), while others focused on long-term hard outcomes such as survival, major adverse cardiac events.

Geographically, the United States and Spain emerged as leaders in trial activity, with substantial contributions also from Germany, the Republic of Korea, and Poland. The global distribution underscores both the widespread interest in cardiac regeneration. Most studies were sponsored by academic or hospital-based investigators, with relatively limited industry and government involvement. This pattern suggests that, while scientific enthusiasm is strong, translation into large-scale, commercially driven trials remains limited. Enrollment sizes varied significantly, ranging from small pilot trials to a large Phase 3 study of umbilical cord-derived mesenchymal stem cells in heart failure (NCT05043610, n=420).

Publications from completed trials consistently demonstrated favorable safety profiles across diverse regenerative strategies, with no evidence of major implant-related, immunologic, or procedure-associated complications. However, efficacy outcomes were variable. The PERISCOPE trial (NCT03798353) confirmed feasibility and immunomodulatory effects but did not show improvements in ventricular function. Similarly, the CAREMI study (NCT02439398) and the AdiFLAP trial (NCT01473433) demonstrated safety without significant or sustained efficacy signals. In contrast, the CIRCULATE-AMI study (NCT03404063) reported a significant and durable reduction in infarct size alongside improvements in LVEF over three years of follow-up. Trials with bone marrow-derived mononuclear cells revealed heterogeneous responses, with substantial LVEF gains in some patients but no benefit in others. Collectively, these findings highlight that while regenerative therapies for cardiac repair are feasible and safe, clinical benefits in terms of ventricular function and remodeling remain inconsistent.

While this analysis provides insights into the ongoing efforts to develop heart regeneration therapies, it is important to note that this dataset is not exhaustive. Many trials, particularly those not registered on ClinicalTrials.gov, may not be captured here. Additionally, the data presented only reflect trials registered up until August 16, 2025, and ongoing studies or trials that have recently commenced may not be included.

Collectively, the findings highlight that regenerative therapy for cardiovascular disease remains an evolving field. Safety has been consistently demonstrated, but efficacy signals are heterogeneous and often modest. Establishing uniform primary and secondary endpoints, including left ventricular ejection fraction, infarct size, major adverse cardiac events, and patient-reported outcomes, will enable meaningful cross-trial comparisons. Precise timing windows for imaging assessments and biomarker collection should be implemented to enhance detection of treatment effects and early identification of responders. Multicenter trials with adequate sample

sizes and adaptive designs will improve statistical power, generalizability, and efficiency, and stronger engagement of industry and government sponsors will be essential to advance promising therapies from investigator-led studies to large-scale phase 3 trials capable of informing clinical practice.

### Acknowledgments

There are no relevant industrial links or affiliations to declare.

### Financial Disclosure Or Funding

The author received no specific financial support for the research, authorship, and publication of this article.

### Conflict Of Interest

The author declares no conflicts of interest.

### Author Contributions

The author contributed to all stages of the preparation of this manuscript for publication.

### Data Availability

Detailed clinical trial data are provided upon reasonable request.

### References

1. World Health Organization. Cardiovascular diseases (CVDs) [Internet]. Geneva: World Health Organization; 2025 Jul 31 [cited 2025 Sep 6]. Available from: [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))
2. Kishino Y, Fukuda K. Unlocking the pragmatic potential of regenerative therapies in heart failure with next-generation treatments. *Biomedicines*. 2023;11(3):915. <https://doi.org/10.3390/biomedicines11030915>
3. Sami N, Parikh MA, Frishman WH, Peterson SJ. Cardiac regeneration from scar to syncytium: mitigating the formation of scar tissue. *Cardiol Rev*. 2023;31(2):90-7. <https://doi.org/10.1097/CRD.0000000000000972>
4. Iamukova L, Alferova E. Personalized cancer vaccines in the clinical trial pipeline. *Asia Pac J Clin Oncol*. 2025 Aug 22. <https://doi.org/10.1111/ajco.70006>
5. Iamukova L. Emerging therapeutic approaches for liver regeneration. *Universum: Medicine and Pharmacology*. 2025;10(127). <https://doi.org/10.32743/UniMed.2025.127.10.20921>
6. Bayes-Genis A, Gastelurrutia P, Monguió-Tortajada M, Cámara ML, Prat-Vidal C, Cediel G, et al. Implantation of a double allogeneic human engineered tissue graft on damaged heart: insights from the PERISCOPE phase I clinical trial. *EBioMedicine*. 2024;102:105060. <https://doi.org/10.1016/j.ebiom.2024.105060>
7. Kwicien E, Drabik L, Mazurek A, Jarocho D, Urbanczyk M, Szot W, et al. Acute myocardial infarction reparation/regeneration strategy using Wharton's jelly multipotent stem cells as an "unlimited" therapeutic agent: 3-year outcomes in a pilot cohort of the CIRCULATE-AMI trial. *Adv Interv Cardiol*. 2022;18(4):476-82. <https://doi.org/10.5114/aic.2022.121125>
8. Sanz-Ruiz R, Casado-Plasencia A, Borlado LR, Fernández-Santos ME, Al-Daccak R, Claus P, et al. Rationale and design of a clinical trial to evaluate the safety and efficacy of intracoronary infusion of allogeneic human cardiac stem cells in patients with acute myocardial infarction and left ventricular dysfunction: the CAREMI trial. *Circ Res*. 2017;121(1):71-80. <https://doi.org/10.1161/CIRCRESAHA.117.310651>
9. Bayes-Genis A, Gastelurrutia P, Cámara ML, Teis A, Lupón J, Llibre C, et al. First-in-man safety and efficacy of the adipose graft transposition procedure (AGTP) in patients with a myocardial scar. *EBioMedicine*. 2016;7:248-54. <https://doi.org/10.1016/j.ebiom.2016.03.027>
10. de Lezo JS, Herrera C, Romero M, Pan M, de Lezo JS Jr, Carmona MD, et al. Functional improvement in patients with dilated cardiomyopathy after intracoronary infusion of autologous bone marrow mononuclear cells. *Rev Esp Cardiol (Engl Ed)*. 2013;66(6):450-7. <https://doi.org/10.1016/j.rec.2012.11.013>
11. Karantalis V, Schulman IH, Balkan W, Hare JM. Allogeneic cell therapy: a new paradigm in therapeutics. *Circ Res*. 2015;116(1):12-5. <https://doi.org/10.1161/CIRCRESAHA.114.305495>
12. Akhtar KH, Khan MS, Baron SJ, Zieroth S, Estep J, Burkhoff D, et al. The spectrum of post-myocardial infarction care: from acute ischemia to heart failure. *Prog Cardiovasc Dis*. 2024;82:15-25. <https://doi.org/10.1016/j.pcad.2024.01.017>
13. Chepeleva EV. Cell therapy in the treatment of coronary heart disease. *Int J Mol Sci*. 2023;24(23):16844. <https://doi.org/10.3390/ijms242316844>