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REVIEW

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The inconclusive superiority debate of allogeneic versus autologous MSCs in treating patients with HFrEF: a systematic review and meta-analysis of RCTs

Omar T. F. Ahmed[1], Ziyad Tarek Ahmed[1], Abdulrahman W. Dairi[1], Maha Saad Zain Al-Abeden[1], Mohammed H. Alkahlot[1], Rana H. Alkahlot[1], Ghazi I. Al Jowf[2,3,5], Lars M. T. Eijssen[3,4,5] and Khawaja Husnain Haider[1,6*]

Abstract

Background Recent randomized controlled trials have consistently demonstrated the safety and potential efficacy of MSC therapy for heart failure patients. This study delves into mesenchymal stem cells' promising potential, offering a beacon of hope for the future of heart failure treatment with reduced ejection fraction (HFrEF).

Methods We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for this systematic review and meta-analysis. We searched four databases and registers for RCTs, including PubMed, EBSCO, clinicaltrials.gov, ICTRP, and other relevant websites. We then selected thirteen RCTs with 1184 participants based on our pre-defined inclusion/exclusion criteria. Two independent assessors extracted the data and performed a quality assessment. The data were then plotted for various outcomes, including death, hospitalization, major adverse cardiac events, pump function parameters, and 6-min walk distance.

Results The safety of MSC-based treatment has been consistently demonstrated with MSCs from autologous (^{Auto}MSCs) and allogeneic (^{Allo}MSCs) sources. This reassuring finding underscores the reliability of MSC-based therapy irrespective of their source. However, ^{Auto}MSCs showed a trend toward greater protective benefits. Subgroup analysis revealed no significant differences between ^{Auto}MSCs and ^{Allo}MSCs in improving LVEF; 0.86% (95% CI − 1.21–2.94%) for ^{Allo}MSCs versus 2.17% (− 0.48%; 95% CI − 1.33–5.67%) for ^{Auto}MSCs. ^{Allo}MSCs significantly reduced end-diastolic volume (LVEDV) by − 2.08 mL (95% CI − 3.52—0.64 mL). Only ^{Allo}MSCs significantly improved 6-min walking distance (6-MWD); 31.88 m (95% CI 5.03–58.74 m) for ^{Allo}MSCs versus 31.71 m (95% CI − 8.91–71.25 m) for ^{Auto}MSCs. The exclusion of studies using adipose-derived cells resulted in even better safety and a significant improvement in LVEF for ^{Allo}MSCs treatment.

Conclusion Our findings suggest that ^{Allo}MSCs are at par with ^{Auto}MSCs in improving functional outcomes in heart failure patients. This underscores the need for future investigations in a larger patient cohort, emphasizing the urgency and importance of further research to fully understand the potential of MSCs in treating heart failure.

Keywords Autologous, Allogeneic, Heart failure, HFrEF, Mesenchymal stem cells, Mesenchymal precursor cells, RCTs

Omar T. F. Ahmed and Ziyad Tarek Ahmed are joint first authors

*Correspondence:
Khawaja Husnain Haider
kh.haider@sr.edu.sa; kh.haider@gmail.com
Full list of author information is available at the end of the article

Introduction

Heart failure (HF) is a chronic progressive medical condition marked by the weakening of the myocardium due to the massive loss of functionally competent cardiomyocytes. The cumulative decline in cardiomyocyte number combined with the inept intrinsic regenerative capacity of the heart, significantly recovering from massive myocardial injury, leads to a progressive decrease in the heart's ability to perform its pump function. Despite its epidemic nature, affecting nearly 1–2% of the population worldwide [1], HF remains incurable and irreversible, causing a significant global health burden besides steadily impairing the affected population's physiological capacity and negatively impacting their quality of life [2–5].

The contemporary advent of mesenchymal stem cells (MSCs) as a living bio-drug for cell-based therapy of the failing heart has demonstrated promise in human studies during advanced phases of clinical trials [6]. Despite their contentious cardiomyogenic differentiation potential as a mechanism of action [7], the observed functional benefits, i.e., attenuated infarct size, reduced fibrosis, and reversal of remodeling reported in the clinical trials using MSC-based therapy in chronically damaged myocardium, have sparked hope in the scientific community [8, 9]. These effects have been ascribed to the soluble and insoluble factors released by MSCs as part of their paracrine activity. MSC-derived paracrine factors, now being studied as a novel cell-free therapy approach, can potentially revolutionize MSC research.

Despite encouraging data from MSCs for cell-based therapy approaches, logistic concerns about their ready-to-use, off-the-shelf availability have hampered their routine use in the emergency room. While autologous MSCs (^{Auto}MSCs) are expected to be immunologically more acceptable than their allogeneic counterparts (^{Allo}MSCs), the latter is a hope in heart failure treatment. Their use surmounts the need to harvest and culture-expand the cells before every treatment, thus overcoming the logistic hurdles associated with using ^{Auto}MSCs. Moreover, ^{Allo}MSCs also facilitate using cells from healthy young donors instead of ^{Auto}MSCs, which may be available from donor patients of advanced age and with multiple comorbidities [10, 11]. ^{Allo}MSCs also offer the distinct benefit of off-the-shelf availability. While human MSCs are generally considered immune-privileged due to their lack of major histocompatibility complex (MHC)II expression, which helps them evade immunosurveillance, they can potentially become immunogenic. This occurs when their immune state shifts in vivo, leading to MHCII induction and the presentation of alloantigens, potentially triggering an immunological memory response. Also, the failure of xenogeneic MSC treatment is often attributed to intractable interspecies differences, which pose significant biological and immunological challenges [12, 13]. The choice of whether to extract MSCs from autologous bone marrow adipose tissue or allogeneic donor tissue is a significant clinical concern. Yet, both have a track record of successfully generating sizable amounts of MSCs [14, 15]. Post-delivery, ^{Auto}MSCs are readily obtained and suffer no immunological rejection. However, most studies use ^{Allo}MSCs, while ^{Auto}MSCs are rarely used in animal or clinical trials. Several factors make allogeneic stem cells more compelling, including donor selection, source diversity, minimal immunogenicity, and readily available off-the-shelf use. ^{Allo}MSCs have also demonstrated encouraging outcomes, even though ^{Auto}MSCs look more convincing for cell-based therapy. This research is significant as it aims to compare the effectiveness of ^{Auto}MSCs and ^{Allo}MSCs in treating HF, providing valuable insights for future treatments.

This meta-analysis examines MSC-based phase I/II/III RCTs (RCTs) involving patients with reduced ejection fraction (HFrEF), aiming to determine source-based effectiveness by comparing ^{Auto}MSCs and ^{Allo}MSCs. We hypothesize the non-inferiority of ^{Allo}MSCs as a safe and adequate living biodrug as a cell-based therapeutic modality. We followed the Preferred Reporting Items for Systemic Review and Meta-analysis (PRISMA) guidelines for systematic reviews and meta-analyses to explore safety and efficacy in terms of functional outcomes, including death, hospitalization, and major adverse cardiac events (MACE) for safety assessment; left ventricle ejection fraction (LVEF), left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV); and 6-min walking distance (6-MWD) for efficacy and functional assessment.

Methodology

Protocol and registration

This review strictly adheres to the PRISMA guidelines, a widely accepted standard for conducting and reporting systematic reviews and meta-analyses in healthcare research. Our research, registered with PROSPERO (CRD42024551327), an international database of prospectively registered systematic reviews in healthcare, can potentially impact HF treatment.

Literature search and study selection process

A systematic and comprehensive literature search on PubMed, EBSCO, ICTRP, and clinicaltrials.gov was meticulously conducted between January and March 2024. The search was conducted through Medical Subject Headings (MeSH) and text search fields. In EBSCO, ICTRP, and clinicaltrials.gov, we used the search terms "Heart Failure," "Congestive Heart Failure," "Left

Ventricular Dysfunction," "Mesenchymal Stem Cells," and "Mesenchymal Precursor Cells" in the text words with appropriate use of the Boolean operator. The search phrases used for PubMed included (heart failure OR congestive heart disease OR left ventricular dysfunction) AND (mesenchymal stem cells OR mesenchymal precursor cells). All the references of eligible studies were screened and reviewed with utmost care for any potential RCTs, ensuring a comprehensive and robust review process.

Inclusion and exclusion criteria

The inclusion criteria for this review were: (1) a phase I/II/III randomized clinical trial, (2) MSC-based therapy as a sole treatment modality and irrespective of the route of administration, and (3) HF patients only. The exclusion criteria were: (1) trials without a clear statement about the cell source, (2) treatment with adjunct interventions (e.g., Coronary artery bypass grafting (CABG), different forms of stem cells, left ventricular assist device), and (3) preserved LVEF (pLVEF), and (4) studies lacking control arms.

Data extraction and outcome of interest

Two authors checked the eligibility of studies and extracted the data to standardized Excel spreadsheets containing several relevant variables. The primary variables included intervention, cell source, sampling sites, country of trial origin, etiology, sample size, gender, age, cell delivery route, imaging modality, and follow-up period. In addition, baseline, follow-up, and mean difference, along with its standard deviation, were extracted at the last follow-up period for LVEF, LVESV, LVEDV, and 6-MWD. The number of deaths, hospitalizations, and MACE (defined in Appendix 2) was recorded at the last follow-up period. The study's corresponding author was approached for any missing data. However, if the corresponding author did not respond, WebPlotDigitizer extracted the missing values [16]. According to their source, studies were assigned to sub-groups into autologous or allogeneic MSCs.

Quality assessment

The quality assessment of included RCTs was evaluated using the Jadad scale using three domains [17]. A study was given one point for randomization and an additional point if the trial mentioned an appropriate method. However, one point was deducted from the evaluation if the randomization was inappropriate. The second domain assessed was blinding, for which the trial was awarded one point for being double-blinded, and an additional point was added when the trial mentioned an appropriate method of double-blinding. Likewise, one point was deducted if the blinding process was inappropriate. Finally, the third domain was the description of withdrawal or dropouts during the trial process for which the trial was given a point. Upon completion of the evaluation process, the scores were added to quantify the quality score for each trial, ranging from zero to five. A trial scoring 0–2 was considered low quality, while those scoring three or more are regarded as high quality.

Statistical analysis

This meta-analysis delved into the clinical trials examining MSCs in treating HF patients. The study employed LVEF, LVESV, LVEDV, and 6-MWD to assess the clinical effectiveness of treatment. Additionally, it used the rate of death, hospitalization, and MACE during clinical trials as insights into the safety profile of the investigated treatment.

As these parameters were measured with consistent units, a weighted mean difference (WMD) meta-analysis was conducted to assess baseline to follow-up changes in LVEF, LVESV, LVEDV, and 6-MWD. On the other hand, the risk ratio (RR) was used to compare safety in the treatment groups to that of the controls. A sub-group analysis was conducted to assess the source-based effect and determine source-related efficacy and safety. Significance of the results was determined using the 95% confidence interval (CI), with studies whose CI crosses the null effect line (i.e., zero) being considered non-significant. The I-square value was used to determine between-studies-heterogeneity. An I-square value of $< 25\%$ indicated low heterogeneity, a value between 25 and 75% showed moderate heterogeneity, while values of $> 75\%$ indicated high heterogeneity. Funnel plots and Egger's regression were used to assess the risk of publication bias. Funnel plots were visually evaluated for asymmetry around the effect line, while Egger's regression indicated a risk of bias with p-values < 0.05 and are provided in the supplementary material (Appendix 1).

Based on the quality of the included studies, the analysis leaving out low-quality studies was conducted to assess overall and subgroup effects, as low-quality studies tend to overestimate the effect size. Additionally, as studies using adipose-derived regenerative cells (ADRCs) consistently reported inferior to no impact, a sensitivity analysis of LVEF, leaving out studies using ADRCs, was conducted to re-assess overall and subgroup effects. Meta-regression analysis for LVEF and 6-MWD parameters was conducted to identify predictors of efficacy and point-specific contributors to heterogeneity using the factor age as a continuous variable and follow-up period, route of administration, cell dose, and concealment of allocation as categorical variables. The

analysis was performed using the statistical package SPSS version 29 (SPSS Inc., Chicago, IL, USA).

Results

Literature review

The four databases yielded 593 results. Most records were retrieved from EMBASE (n = 335), followed by PubMed (n = 197), clinicaltrials.gov (n = 96), and ICTRP (n = 59). Filters excluded 140 results; from the remaining records, the authors identified duplicates (n = 132) before screening. From the screened records (n = 321), trials with irrelevant abstracts (n = 181) and non-human trials (n = 114) were excluded. A total of 26 potential candidate trials were retrieved except for one. The retrieved 25 trials were then screened with our inclusion/exclusion criteria, from which crossover trials (n = 2), non-controlled trials (n = 3), trials with additional intervention (n = 9), and non-English records (n = 1) were excluded. Additionally, three trials were identified through reference searching of eligible records. Subsequently, the final number of 13 trials was included in our review for analysis (Fig. 1).

Description of the trials included in the review and meta-analysis

Table 1 gives the salient features of the thirteen trials in this review. Concerning autologous and allogeneic cell sources, six trials used autologous MSCs (n = 6), while seven studies used allogeneic MSCs (n = 7). The trials used MSCs from various sampling sites, including bone marrow (n = 7), umbilical cord (n = 2), and adipose tissue (n = 4). All the trials were placebo-controlled or sham-controlled. The total number of patients in the 13 included RCTs was 1184, with 657 patients in the intervention group and 527 patients in the control group. Male participants dominated the samples (n = 933). A wide range of sample sizes was noticeable between the trials, ranging from 12 to 265 in the treatment group and 12 to 272 in the control group. The follow-up period

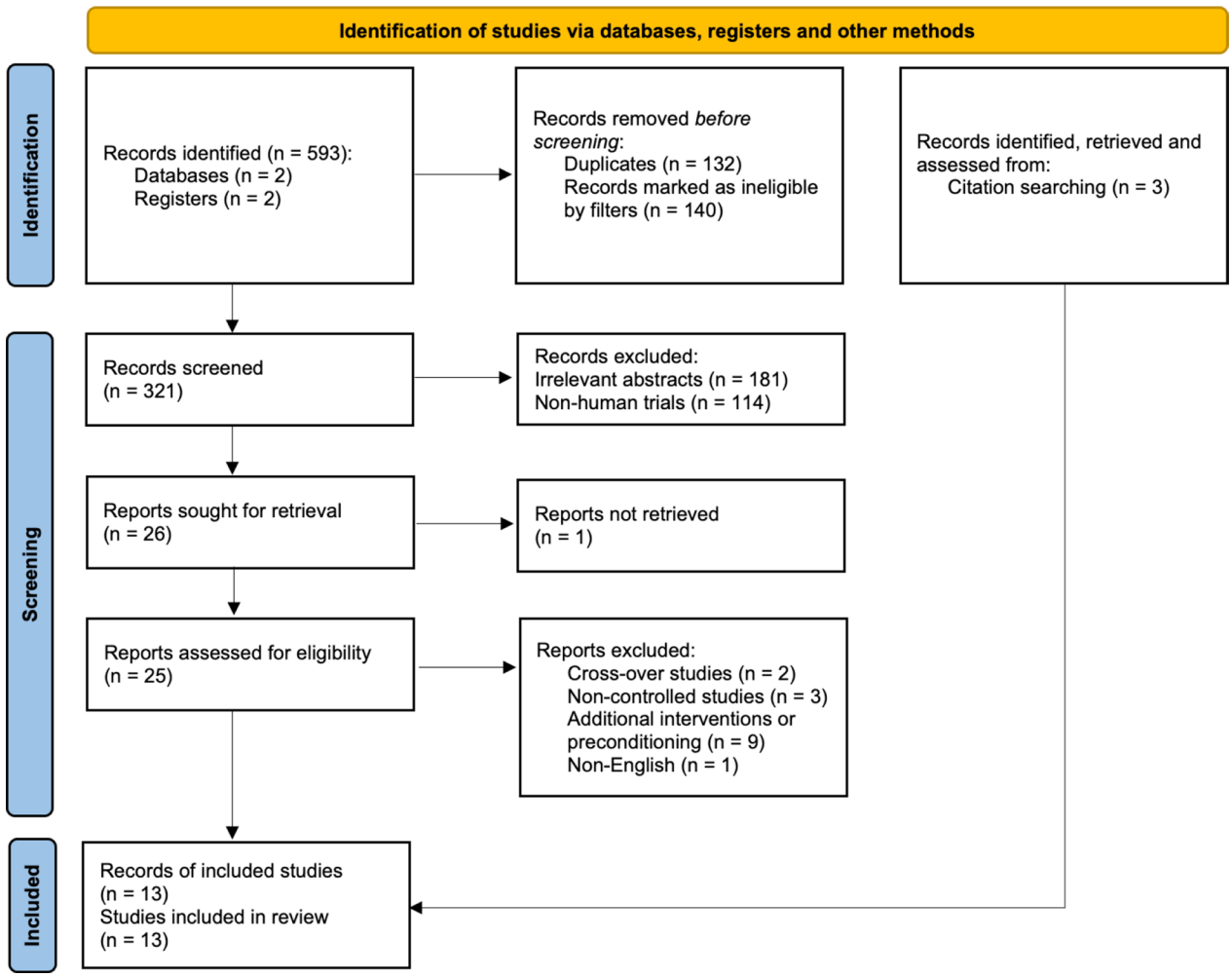

Fig. 1 The PRISMA flow diagram for the screening and selection of eligible trials

Table 1 Characteristic features of the thirteen RCTs included in the meta-analysis. Quality assessment (risk of bias) using the Jadad Score

Study	Arm	Source	Sampling site	Country	Etiology	Sample size	Males	Age	RoA	Imaging modality	F/U (mo)
MSC-HFT [19]	Intervention	Autologous	Bone marrow (Iliac crest)	Denmark	Ischemic HF	40	36	66.1 (7.7)	IM	MRI or CT	6
	Control					20	14	64.2 (10.6)			
CONCERT-HF [20]	Intervention	Autologous	Bone marrow	USA	Ischemic Cardiomyopathy	29	27	61.7 (6.7)	TE	MRI	12
	Control					32	31	63.1 (8.8)			
Xiao et al. [21]	Intervention	Autologous	Bone marrow (Posterior iliac spines)	China	Dilated Cardiomyopathy	17	12	51.6 (12.2)	IC	Echo	12
	Control					20	14	54.4 (11.6)			
TAC-HFT [22]	Intervention	Autologous	Bone marrow (Iliac crest)	USA	Ischemic Cardiomyopathy	22	18	57.1 (10.6)	TE	MRI or CT	12
	Control					22	10	60 (12.0)			
Athena Trials [18]	Intervention	Autologous	Abdominal adipose tissue	USA	Ischemic Cardiomyopathy	17	16	64.1 (8.2)	IM	Echo	6
	Control					14	13	65.7 (7.3)			
PRECISE Trial [23]	Intervention	Autologous	Abdominal adipose tissue	USA	Ischemic Cardiomyopathy	21	17	65.8 (6.3)	TE	Echo	36
	Control					6	4	55.7 (6.1)			
RIMECARD Trial [24]	Intervention	Allogeneic	Umbilical cord	Chile	Ischemic or Nonischemic Cardiomyopathy	15	12	57.33 (10.05)	IV	Echo	12
	Control					15	14	57.20 (11.64)			
Danish phase II [25, 26]	Intervention	Allogeneic	Abdominal adipose tissue	Denmark	Ischemic HF	54	44	67.0 (9.0)	IM	Echo	6/12
	Control					27	24	66.6 (8.1)			
Butler et al. [27]	Intervention	Allogeneic	Bone marrow	USA	Nonischemic Cardiomyopathy	12	13	47.3 (12.8)	IV	MRI	3
	Control					12					
Perin et al. [28]	Intervention	Allogeneic	Bone marrow (Posterior iliac crest)	USA	Ischemic or Nonischemic HF	45	2	60.1 (8.8)	TE	Echo	12
	Control					15	4	62.7 (11.2)			
Zhao et al. [29]	Intervention	Allogeneic	Umbilical cord	China	Ischemic or Nonischemic Cardiomyopathy	30	24	52 (16)	IC	Echo	6
	Control					29	19	53 (11)			
SCIENCE [25, 26]	Intervention	Allogeneic	Abdominal adipose tissue	Denmark	Ischemic HF	90	84	66.4 (8.1)	IM	Echo	6/12
	Control					43	38	64.0 (8.8)			
DREAM-HF [30]	Intervention	Allogeneic	Bone marrow	Canada, USA	Ischemic or Nonischemic HF	265	222	62.7 (10.9)	TE	Echo	12
	Control					272	221	62.6 (10.4)			

varied between the trials, with some reaching four years for safety assessment; however, 3–12 months were assessed to reduce heterogeneity. Most trials assessed LVEF using echocardiography (n = 9), while others used cardiac CT or MRI (n = 4). Trans-endocardial (n = 5) and intramyocardial (n = 4) routes were the standard modes of cell delivery, followed by intravenous (n = 2) and intracoronary (n = 2) routes. The ATHENA trials consist of two parallel prospective trials [18].

The Jadad score for the trials ranged between 2 and 5. Although all trials were of high quality (i.e., ≥ 3), one study each by Zhao et al. and Xiao et al. scored two points. As a result, these studies have been excluded from the primary meta-analysis to avoid effect overestimation. Table 2 shows a detailed assessment of the included trials.

Meta-Analysis for safety and efficacy parameters

Death, hospitalization, and major adverse cardiac events

All RCTs included in the study consistently reported death, hospitalization, and MACE. The overall risk ratio (RR) for death was 0.89 (95% CI 0.47–1.70), 0.92 (95% CI 0.35–2.42) for the allogeneic subgroup, and 0.79 (95% CI 0.28–2.28) for the autologous subgroup (Fig. 2). Heterogeneity was low, with an $I^2 = 0.03$. Analysis using funnel plot and Egger's regression (p-value = 0.864) demonstrated a low risk of publication bias (Supplementary Table 1 and Fig. 1). The overall RR for hospitalization was 0.90 (95% CI 0.72–1.14). Subgroup analysis showed a significant reduction in hospitalization with autologous MSC treatment, with an RR of 0.65 (95% CI 0.42–0.99) (Fig. 3). Low heterogeneity was observed with an $I^2 = 0.09$ and a low risk of publication bias (p-value = 0.894) (Supplementary Table 2 and Fig. 2). Regarding MACE, the pooled RR of MACE after MSC-based treatment using either allogeneic or autologous type of cells is 1.02 (95% CI 0.86–1.21). Subgroup analysis showed a RR of 1.06 (95% CI 0.87–1.29) for the allogeneic source and 0.90 (95% CI 0.63–1.30) for the autologous source. The studies showed no heterogeneity with an $I^2 = 0.00$ (Fig. 4). Funnel plot and Egger's regression (p-value = 0.685) indicated a low risk of publication bias, and between-subgroup heterogeneity was similar overall (Supplementary Table 3 and Fig. 3).

Cardiac function parameters

The LVEF and its change from baseline to the follow-up period were reported in almost all RCTs included except for the PRECISE trial by Perin et al. Overall, MSC treatment improved LVEF by 1.44% (95% CI −0.42–3.29%) compared to controls, with high heterogeneity ($I^2 = 0.90$). The funnel plot and Egger's regression analysis indicated a low risk of publication bias (p-value = 0.653), and between-subgroup heterogeneity was similar to the overall (Supplementary Table 4, Fig. 4). Subgroup analysis revealed non-significant improvements of 0.86% (95% CI; -1.21–2.94%) with allogeneic source and 2.17% (95% CI; −1.33–5.67%) with autologous MSCs (Fig. 5). Interestingly, as studies using ADRCs consistently showed inferior results, their exclusion showed a significant improvement of 2.03% (95% CI 0.19–3.87%) with allogeneic MSC treatment (Fig. 6). A meta-regression analysis was conducted to identify possible contributors to heterogeneity using the predetermined variables. Expectedly, all the variables (i.e., age, follow-up period, route of administration, cell dose, and concealment of allocation)

Table 2 The Jadad Score for risk of bias (Quality) assessment

Study	Jadad scale items					Total	Quality
	J1	J2	J3	J4	J5		
MSC-HF [19]	1	1	1	1	0	4	High
RIMECARD [24]	1	1	1	1	0	4	High
CONCERT-HF [20]	1	1	1	1	1	5	High
Danish phase II [25, 26]	1	1	1	1	0	4	High
Butler et al. [27]	1	1	0	0	1	3	High
[28] [28]	1	1	1	1	1	5	High
Xiao et al. [21]	1	1	0	0	0	2	Low
TAC-HFT [22]	1	1	1	1	0	4	High
Zhao et al. [29]	1	0	1	0	0	2	Low
SCIENCE [25, 26]	1	1	1	0	1	4	High
PRECISE [23]	1	1	1	1	0	4	High
DREAM-HF [30]	1	0	1	1	1	4	High
ATHENA [18]	1	0	1	1	1	4	High

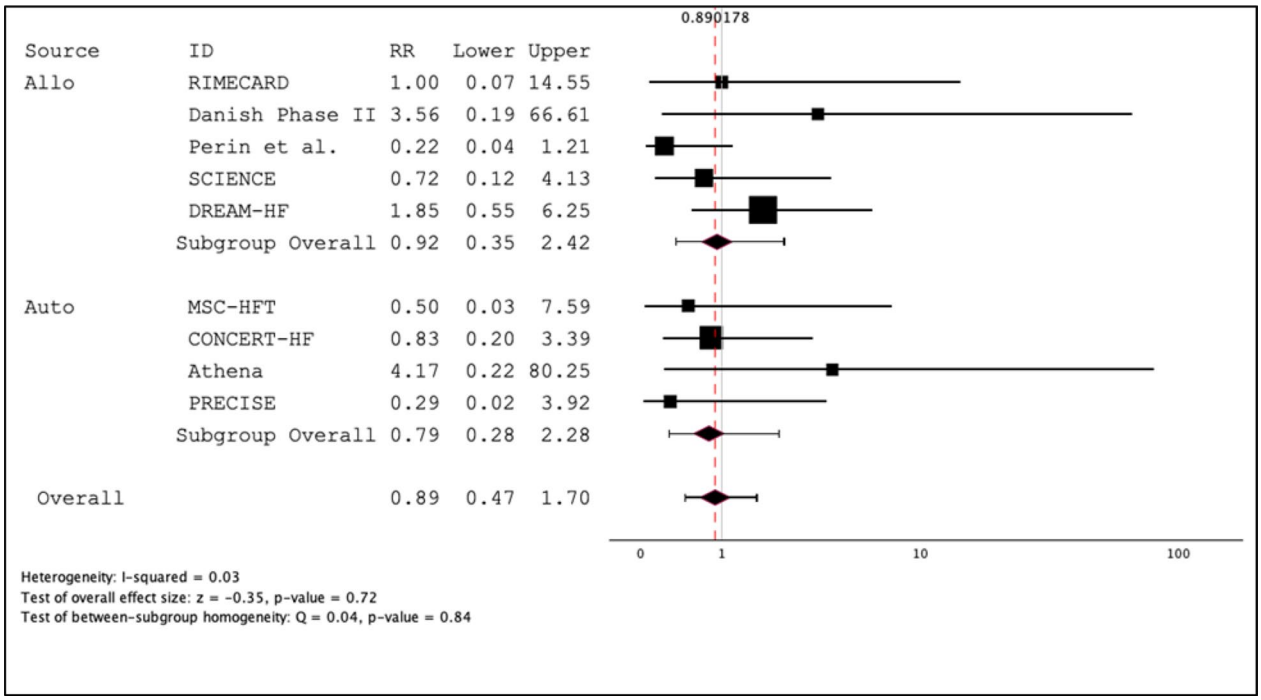

Fig. 2 Forest plot of the risk ratio (RR) for death meta-analysis

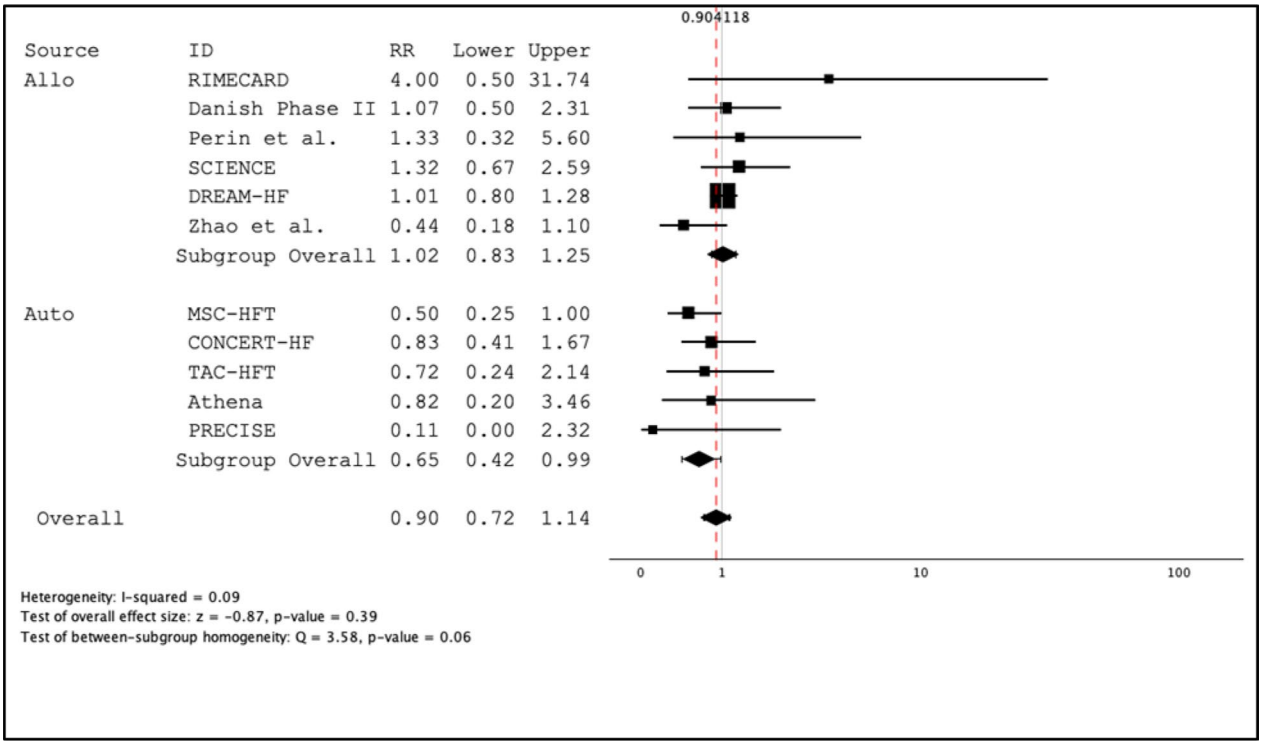

Fig. 3 Forest plot of the risk ratio (RR) for hospitalization meta-analysis

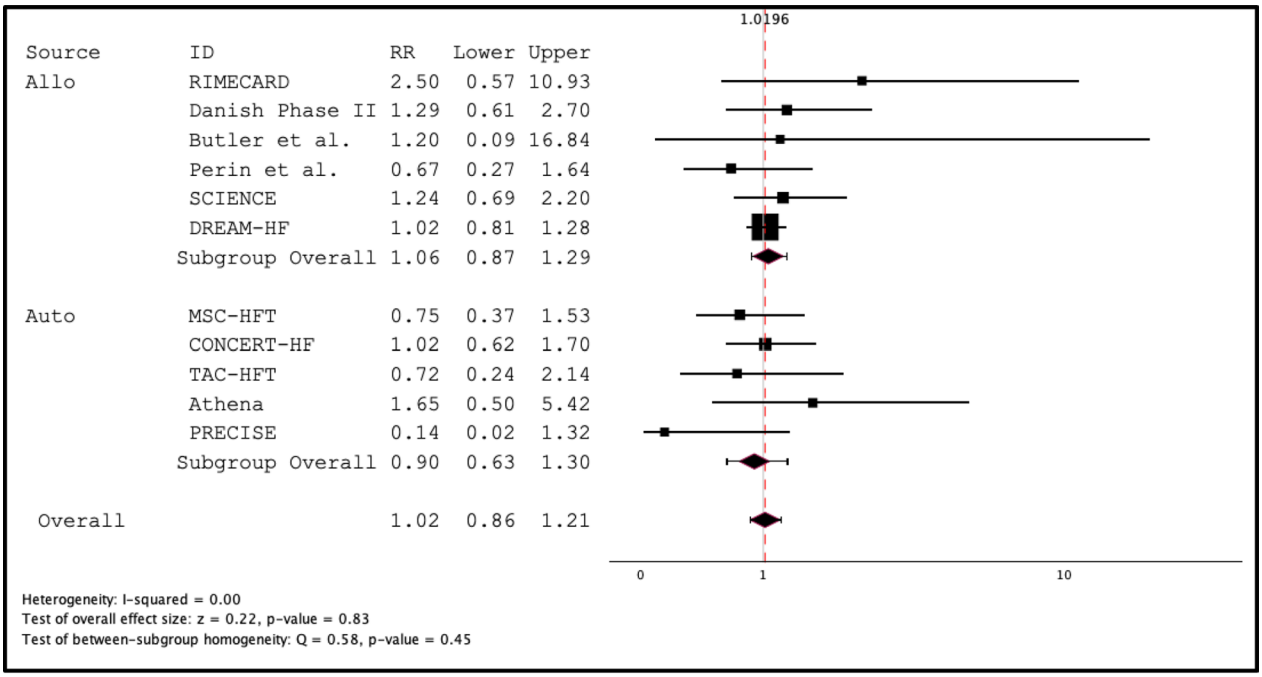

Fig. 4 Forest plot of the risk ratio (RR) for MACE meta-analysis

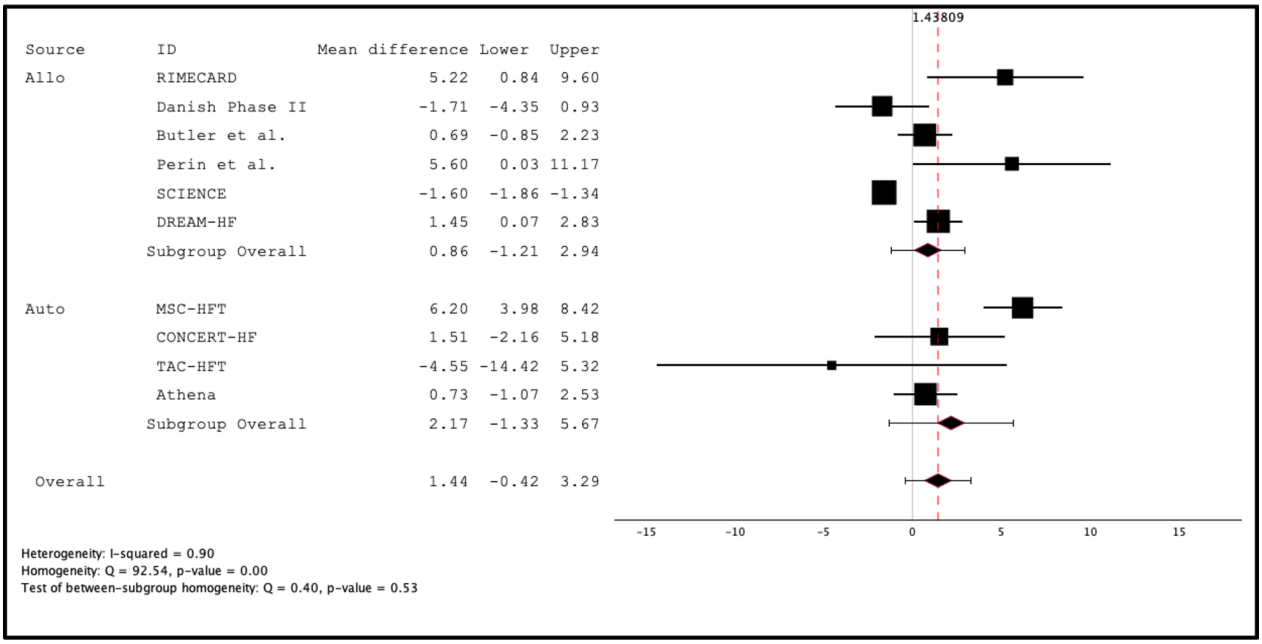

Fig. 5 Forest plot of the weighted mean difference (WMD) for LVEF meta-analysis

were significant predictors of the relationship and contributed to the high heterogeneity between the studies (Supplementary Table 9). Galbraith plot depicts potential outliers that mainly contribute to the heterogeneity, namely MSC-HFT, Butler et al., SCIENCE, and DREAM-HF (Fig. 7).

Further analysis showed no significant differences between groups in reducing LVESV, with an overall WMD of − 5.70 mL (95% CI − 13.26–1.85 mL) (Fig. 8).

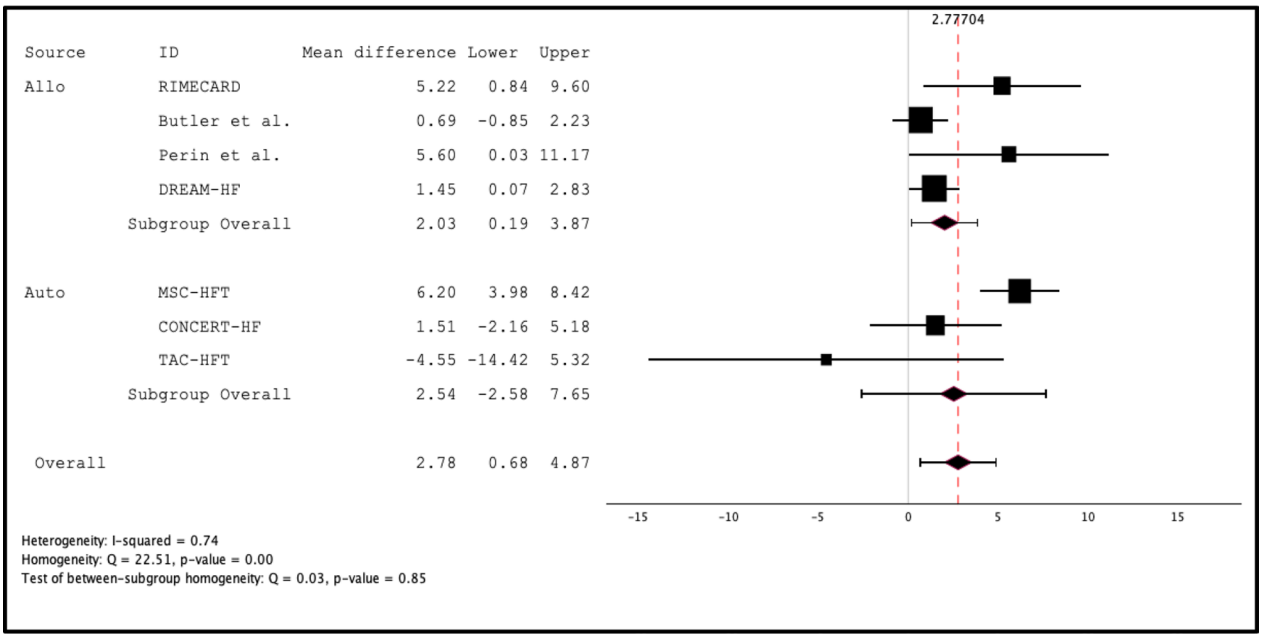

Fig. 6 Forest plot of the weighted mean difference (WMD) for LVEF meta-analysis excluding ADRCs trials

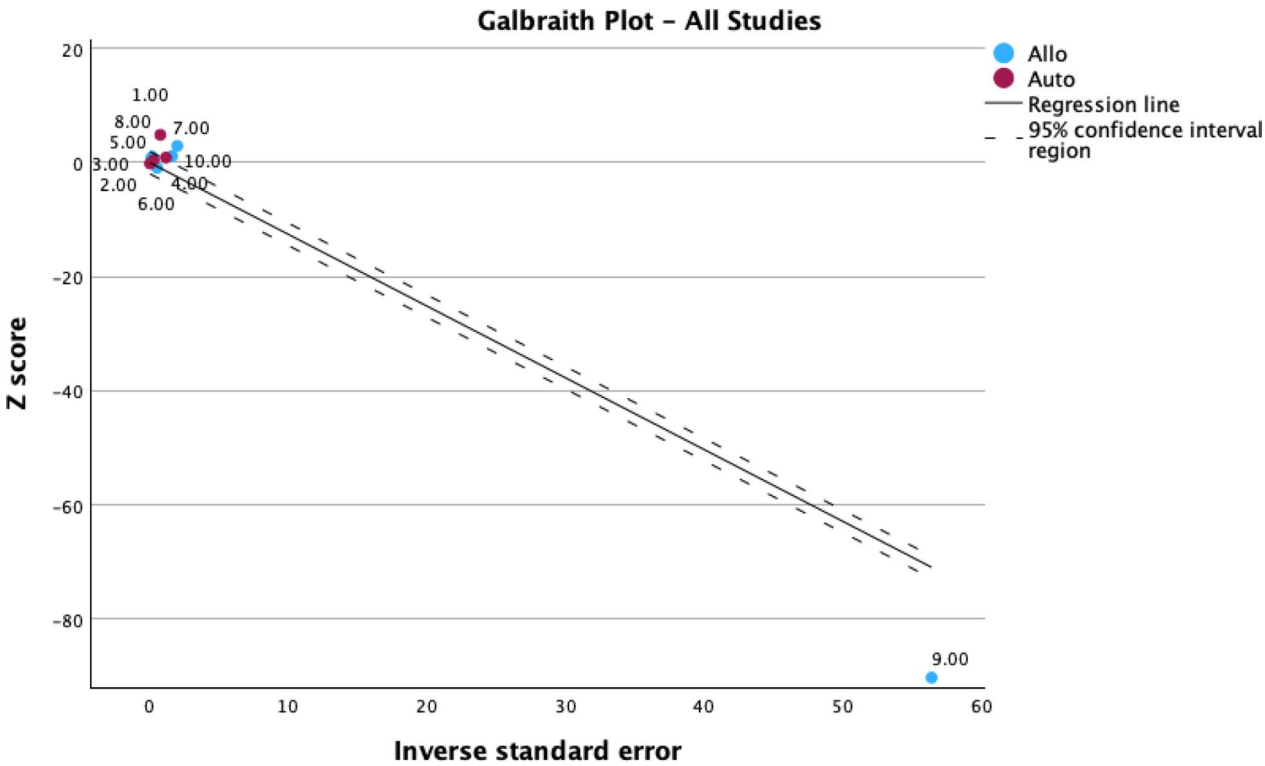

Fig. 7 Galbraith plot of the LVEF meta-analysis, with studies numbered in order

A high heterogeneity between studies was present ($I^2 = 0.90$). The funnel plot showed a risk of publication bias. However, Egger's regression analysis indicated a low risk of publication bias (p-value = 0.350) (Supplementary Table 5, Fig. 5). On the other hand, allogeneic MSC treatment resulted in a significant

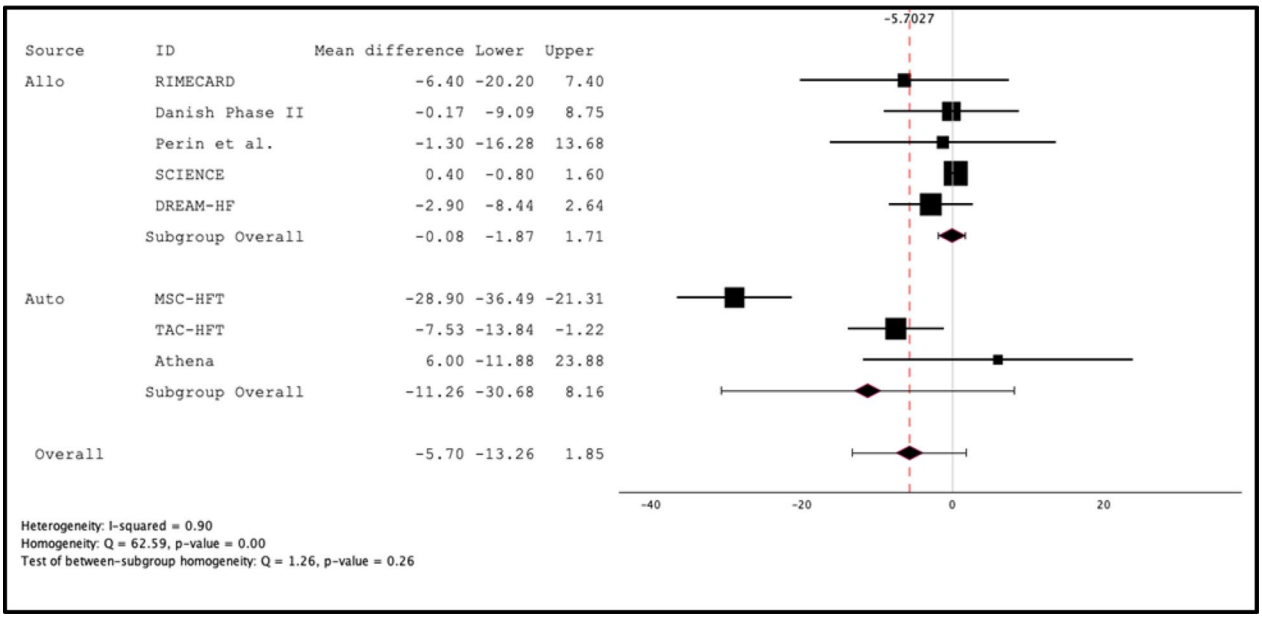

Fig. 8 Forest plot of the weighted mean difference (WMD) for LVESV meta-analysis

reduction in LVEDV, with a subgroup WMD − 2.08mL (95% CI − 3.52-(− 0.64) mL) (Fig. 9). Moderate heterogeneity with $I^2 = 0.35$ was observed. Egger's regression analysis indicated a low risk of publication bias (p-value = 0.121), although the funnel plot showed a risk of bias (Supplementary Table 6, Fig. 6).

6-Minute walking distance test

Only four RCTs included in the analysis, each with six arms, documented the changes observed from baseline to the follow-up period. The RIMECARD, Athena, PRECISE, and DREAM-HF trials did not consider the 6-MWD as an end-point in their respective trials. The 6-MWD is a widely used measure of functional capacity and is an essential indicator of the patient's ability to

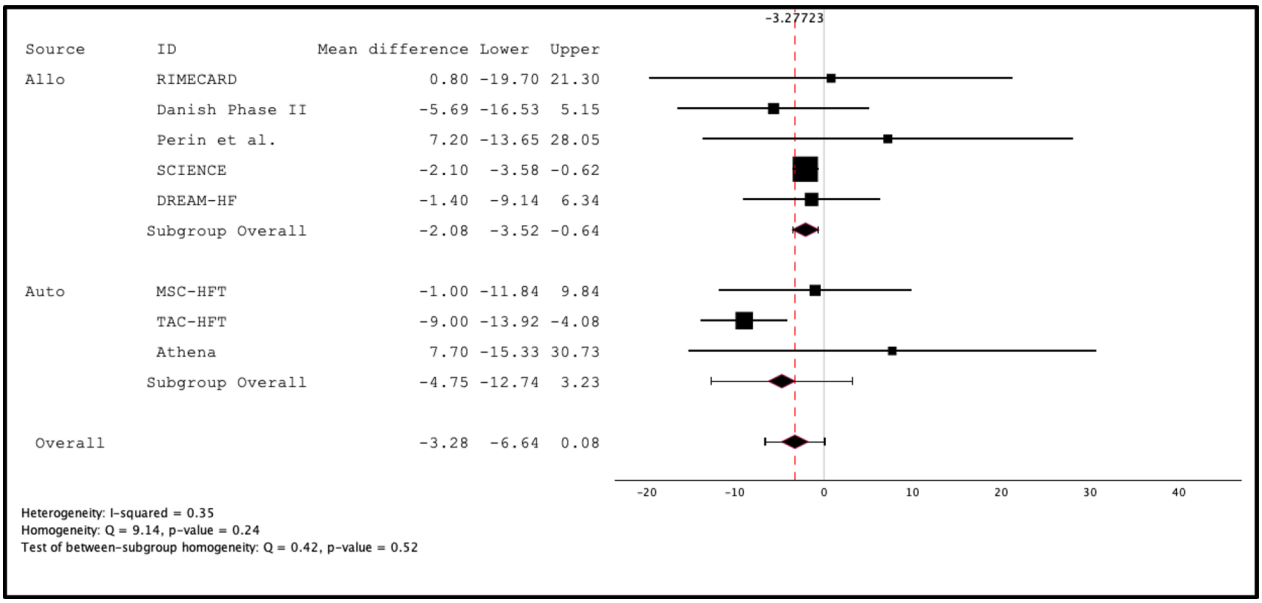

Fig. 9 Forest plot of the weighted mean difference (WMD) for LVEDV meta-analysis

perform daily activities. Although the remaining trials measured the distance at baseline and follow-up, they did not report any data on the change. Despite multiple attempts to contact the corresponding authors for the necessary information, no response has been received thus far. Overall, MSC treatment increased the 6-MWD by 29.48 m (95% CI 10.03–48.93 m), with no heterogeneity ($I^2 = 0.00$) (Fig. 10). The funnel plot and Egger's regression suggested a low risk of publication bias (p-value = 0.754), with consistent findings across subgroups. Subgroup analysis showed higher heterogeneity between studies using autologous MSCs (Supplementary Table 7, Figs. 7 and 8). Subgroup analysis further demonstrated a significant increase in 6-MWD compared to controls, with 31.88 m (95% CI 5.03–58.74 m) for allogeneic sources and 31.17 m (95% CI −8.91–71.25 m) for the autologous source (Fig. 9). A summary of the effects of both treatments on the primary parameters is presented in Table 3.

Discussion

With the rapid emergence of regenerative medicine, various types of stem cells have progressed to the final phases of clinical trials. Notably, some of these cell types, particularly mesenchymal stem cells (MSCs), have already received clinical approval for use as living biodrugs, such as Prochymal (Osiris Therapeutics, Canada), Cartistem (Medipost Co Ltd, Korea), Stempeucel (Stempeutics Research), and Cellgram-AMI (FCB Pharmicell, South Korea) (Alliance for Regenerative Medicine; https://alliancerm.org/available-products/). However, their performance continues to be monitored closely. Our systematic review of published randomized controlled trials (RCTs) and meta-analysis aims to compare the clinical safety and efficacy of autologous (^{Auto}MSCs) and allogeneic

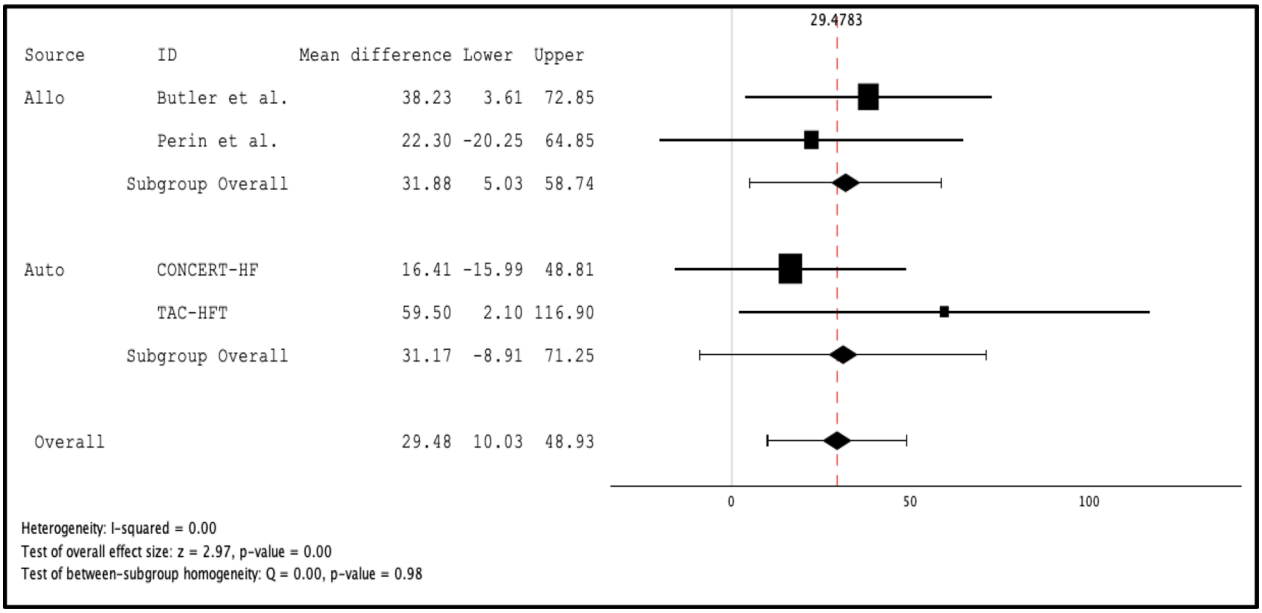

Fig. 10 Forest plot of the weighted mean difference (WMD) for 6-MWD meta-analysis

Table 3 A summary of the effects of both treatments on the primary parameters

Summary of effect sizes					
Parameter\Source	**^{Auto}MSCs**		**^{Allo}MSCs**		**Comparison Results**
	Result	95% CI	Result	95% CI	
MACE	0.90 RR	0.63–1.30	1.06 RR	0.87–1.29	Safer trend with ^{Auto}MSCs treatment
LVEF	2.17%	−1.33–5.67	0.86%	−1.21–2.94	Non-significant difference between groups, with a trend of superior efficacy with ^{Auto}MSCs treatment
6-MWD	31.17 m	−8.91–71.25	31.88 m	5.03–58.74	Significant improvement with ^{Allo}MSCs treatment compared to non-significant improvement with ^{Auto}MSCs treatment

MSCs (^{Allo}MSCs). The key findings of our study include: (1) this is the first systematic review and meta-analysis to compare ^{Auto}MSCs with ^{Allo}MSCs for cardiovascular applications directly; (2) as autologous cells are generally regarded as a safer and more practical choice, most reported clinical trials have focused on ^{Auto}MSCs, resulting in limited evidence regarding efficacy based on the source; (3) both ^{Allo}MSCs and ^{Auto}MSCs exhibited similar safety profiles; and (4) our analysis demonstrated the non-inferiority of ^{Allo}MSCs compared to their autologous counterparts.

Different mechanisms contribute to HFpEF than those of HFrEF; hence, the mechanisms by which cell therapy exerts its effects in both states appear to differ [31, 32]. Therefore, we restricted our study to the group with HFrEF for analysis. The unique cell biology and morphological features of MSCs delineate them from other stem cell types used in cell-based therapy and distinguish the mechanisms through which they exert their effects [33]. Studies utilizing additional concurrent interventions were not included to eliminate confounding effects. Our safety analysis, which included parameters such as death, hospitalization, and MACE, indicated that both ^{Auto}MSCs and ^{Allo}MSCs are safe. However, ^{Auto}MSCs showed protective effects after excluding ADRCs, with a 35% reduction in hospitalization rate. This thorough safety analysis, a cornerstone of our study, reassures the reader of the reliability and robustness of our findings, instilling confidence in the study's conclusions.

LVEF was significantly improved with ^{Allo}MSCs compared to non-significant improvement with ^{Auto}MSCs. Additionally, LVEDV showed a significant reduction with ^{Allo}MSCs, and ^{Allo}MSCs significantly improved the 6-MWD compared to ^{Auto}MSCs by 31.88 m. Although preclinical studies have extensively used both ^{Auto}MSCs and ^{Allo}MSCs, none of these studies have directly compared both types of MSCs [34–38]. Similarly, translational studies yielded the same conclusions without head-to-head comparisons between the two cell types [39–42]. The POSEIDON trial, a phase I/II study in 30 patients, is the only one that directly compared ^{Auto}MSCs to ^{Allo}MSCs [43]. It is also a dose-escalation study in which 20 million, 100 million, or 200 million cells were delivered through trans-endocardial injection. The results indicated that both ^{Auto}MSCs and ^{Allo}MSCs were safe and exhibited potential regenerative bioactivity. However, it was excluded from our analysis due to it lacking a control group [43]. One systematic review and meta-analysis, including 82 studies from large animal models of ischemic heart disease, showed significant improvement in LVEF irrespective of the cells' origin [44]. A couple of recently published systematic reviews and meta-analyses have reported the non-significant superiority of ^{Auto}MSCs over their ^{Allo}MSCs counterparts in the functional improvement and pain relief in osteoarthritis and spinal cord injury [45, 46]. It is important to mention that the SCIENCE II pilot trial was published after the conduction of our current study. Interestingly, the study used allogeneic stem cells and showed meaningful increases in LVEF of 6.5%, while LVESV significantly decreased by 25 mL. These results support the current findings of our study on the efficacy and possible superiority of ^{Allo}MSCs.

The present study did not primarily intend to assess efficacy, as evidence already exists in this regard [6, 47–49]. Instead, it provides a head-to-head comparison of autologous and allogeneic MSCs in treating HFrEF. As addressed by previous studies, MSC treatment for HF is safe and effective. The results of our analysis are in line with these findings. MSC-based treatment, regardless of the source, was found to be safe. Improvements in 6-MWD are significant, and an increase of more than 30 m crossed is a meaningful result for HF patients that can positively impact their quality of life. However, it is impossible to draw conclusive evidence from this data, given the small sample size and number of studies included in the analysis. Such results should be interpreted with caution and considered preliminary evidence. Although an improvement of 2.78% in LVEF was found overall, along with similar subgroup results, the question remains whether these improvements are meaningful. Clinically, an increase of $\geq 5\%$ in LVEF is considered meaningful [50–52]. So far, studies that have conducted rigorous analysis have not found such an outcome using MSCs in HF. This highlights the current state of the art in cell therapy for HF and the need to recognize it as an adjuvant rather than sole treatment. Translating MSC-based therapies into clinical practice faces significant practical challenges, including standardizing cell preparation following good manufacturing practices (GMP), ensuring consistent quality control and potency, and curtailing variability in therapeutic outcomes. Additionally, logistical hurdles, such as large-scale cell production, storage, transportation, and off-the-shelf ready-to-use availability, complicate their routine clinical use. Regulatory complexities and high costs also limit accessibility and scalability.

Despite promising results, the lack of comprehensive cost-effectiveness analyses hinders informed decision-making regarding their adoption. Future research must prioritize economic evaluations to assess the feasibility of MSC-based therapies in real-world settings, ensuring they deliver both clinical benefits and sustainable value for healthcare systems. As of the time of writing this revised version of the manuscript, no new advanced-phase clinical study has been reported providing a

head-to-head comparison of ^{Auto}MSCs vs. ^{Allo}MSCs. This lack of direct comparison evidence has already hindered a definitive conclusion about the superiority of one over the other. The use of ^{Auto}MSCs faces several potential limitations. Firstly, sourcing sufficient quantities of ^{Auto}MSCs from patients is challenging, particularly in cases where the source is compromised, such as in thin individuals or patients with myelofibrosis. Secondly, the biological activity and stemness of ^{Auto}MSCs decrease with age and the morbid health status of the donor, thus making it a challenge to acquire enough healthy and therapeutically effective ^{Auto}MSCs. [53], Therefore, it is challenging to acquire enough healthy and therapeutically effective ^{Auto}MSCs [54, 55]. Moreover, ^{Auto}MSCs are logistically time-intensive, requiring longer waiting to isolate, purify, and expand the cells to achieve the required cell number, rendering their emergency room utility very minimal and difficult in treating acute conditions, e.g., stroke and myocardial infarction. On the contrary, ^{Allo}MSCs provide an off-the-shelf, ready-to-use availability of cells to overcome logistic issues. Also, their use may help avoid donor age and health-related issues. Although most in vitro studies have highlighted the immunosuppressive properties of ^{Allo}MSCs, several studies have evidenced their immunogenicity, which is accentuated in the proinflammatory milieu [56]. Preclinical investigations showed alloantibodies after ^{Allo}MSCs delivery [57, 58] besides an increased number of neutrophils, monocytes, and T cells at the site of intracranial injection of ^{Allo}MSCs [59]. There is evidence of productive allorecognition by B cells and anti-donor T-cell and NK-cell responses to ^{Allo}MSCs delivery in immuno-competent rhesus macaques [60]. The magnitude of the host allo-response was influenced by the degree of MHC class I and II mismatch between the donor and host.

Adipose-derived regenerative cells (ADRCs) are valued for their abundance and ease of availability with minimal invasiveness, making them attractive candidates for clinical applications. Their paracrine effects, similar to BM-MSCs, promote angiogenesis, reduce apoptosis, and enhance immunomodulation despite limited cardiomyogenic differentiation. Preclinical studies have demonstrated significant cardiac improvements with ADRCs, but phase I trials in HF patients reported limited functional gains while confirming safety. In comparison, BM-MSCs may offer better efficacy in treating HFrEF. These findings necessitate phase II/III studies focusing on cell dose-escalation to establish a dose–response relationship for MSCs as living bio-drugs for better prognosis [61].

Although the study demonstrated promising safety and efficacy data with improved functional outcomes, such as the 6-MWD, it has certain limitations. For instance, inconsistencies in reporting functional parameters, including the 6-MWD and New York Heart Association (NYHA) class during follow-up, hindered the accurate assessment of valuable clinical outcomes. Furthermore, trials exploring head-to-head comparison of ^{Auto}MSCs vs. ^{Allo}MSCs via multi-arm comparison were excluded, primarily due to the absence of a control arm. Additionally, variability in clinical design elements, such as the administration route, source, sampling site, and follow-up duration, may introduce bias and impact result reliability. The findings offer initial insights into the dose–response relationship to inform future clinical trial designs.

It is pertinent to mention that few clinical trials have observed the development of donor-specific antibodies in ^{Allo}MSCs recipients. This development could potentially lead to the rejection of the ^{Allo}MSCs, which would significantly impact the safety and efficacy of the treatment. Moreover, there is a lack of clinical evidence about the safety and effectiveness of the treatment after developing these antibodies. [62]. Other studies indicate that no patients treated with allogeneic mesenchymal progenitor cells (MPCs) produced donor HLA-specific antibodies [63, 64]. These data suggest that alloantibodies formation may not be as critical as initially believed but depends on the phenotype of the administered cells and the specific disease. However, the implications of developing donor-specific allo-antibodies need to be evaluated over more extended periods, besides the tolerability and efficacy of single and repeated administration of ^{Allo}MSCs, before definitive conclusions can be made. The development of donor-specific allo-antibodies could potentially lead to rejection of the ^{Allo}MSCs, which would significantly impact the safety and efficacy of the treatment.

Conclusion

In conclusion, despite progress to the advanced phases of clinical assessment, the debate between ^{Auto}MSCs and ^{Allo}MSCs in treating patients with HFrEF remains inconclusive. Both have their pros and cons. While the immunosuppressive properties and lower immunogenicity render ^{Auto}MSCs a superior choice, the challenges of sourcing them from elderly patients with comorbidities and the logistical issues they present make ^{Auto}MSCs less practical. On the other hand, off-the-shelf, ready-to-use availability is a big plus with ^{Allo}MSCs. The published preclinical and clinical data on the immunogenicity and protective effects of ^{Allo}MSCs are insufficient and inconsistent. Future research must address several issues, including understanding the dynamic fate of implanted ^{Allo}MSCs, rejection by the recipient, maintenance of stemness, and reparability. Concluding these issues is crucial for establishing ideal cell-based therapy in clinical settings. However, the inconsistent conclusions drawn

from various studies regarding the therapeutic effects of all MSCs highlight the need for further research.

Abbreviations

ADRCs	Adipose-derived regenerative cells
CMs	Cardiomyocytes
HF	Heart failure
HFrEF	HF with a reduced ejection fraction
HFpEF	HF with a preserved ejection fraction
LVEF	Left ventricle ejection fraction
LVESV	Left ventricular end-systolic volume
LVEDV	Left ventricular end-diastolic volume
MACE	Major adverse cardiac events
MHC	Major histocompatibility complex
MPCs	Mesenchymal progenitor cells
MSC_S	Mesenchymal stem cells
^{Allo}MSCs	Allogenic MSCs
^{Auto}MSCs	Autologous MSCs
6-MWD	6-Minute walking distance
PRISMA	Preferred reporting items for systemic review and meta-analysis
RR	Risk ratio
RTCs	Randomized control trials
WMD	Weighted mean difference

Supplementary Information

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Additional file 1 (DOCX 953 kb)

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Author contributions
K.H.H. designed and produced the study and its methodology. O.T.F.A. and Z.T.A. performed database research and screened the extracted records against eligibility criteria. A.W.D., M.H.A and R.H.A. performed data extraction and plotting. O.T.A., A.W.D., and M. S. Z. reviewed and validated the extracted data. Z.T.A. and A.W.D. performed the quality assessment of the included trials. Z.T.A., M.S.Z., L.M.T.E, and G.I.J. conducted the statistical analysis. O.T.A. and K.H.H. drafted the first manuscript. All authors contributed to the final manuscript. K.H.H., O.T.A., Z.T.A., L.M.T.E, and G.I.J. reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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Declarations

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Author details
[1]College of Medicine, Sulaiman Alrajhi University, 52726 Al-Bukairiyah, Saudi Arabia. [2]Department of Public Health, College of Applied Medical Sciences, King Faisal University, 31982 Al-Ahsa, Saudi Arabia. [3]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience (MHeNs), Faculty of Health, Medicine and Life Sciences, Maastricht University Medical Centre, 6200 MD Maastricht, The Netherlands. [4]Department of Bioinformatics – BiGCaT, School of Nutrition and Translational Research in Metabolism (NUTRIM), Faculty of Health, Medicine and Life Sciences, Maastricht University, 6200 MD Maastricht, The Netherlands. [5]European Graduate School of Neuroscience, Maastricht University, 6200 MD Maastricht, The Netherlands. [6]Cellular and Molecular Pharmacology, Sulaiman Alrajhi Medical School, PO Box 777, 51941 Al Bukairiyah, Saudi Arabia.

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