Dose-response relationship of MSCs as living Bio-drugs in HFrEF patients: a systematic review and meta-analysis of RCTs

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Abstract

Background Mesenchymal stem cells (MSCs) have emerged as living biodrugs for myocardial repair and regeneration. Recent randomized controlled trials (RCTs) have reported that MSC-based therapy is safe and effective in heart failure patients; however, its dose-response relationship has yet to be established. We aimed to determine the optimal MSC dose for treating HF patients with reduced ejection fraction (EF) (HFrEF).

Methods The preferred reporting items for systematic reviews and meta-analyses (PRISMA) and Cochrane Handbook guidelines were followed. Four databases and registries, i.e., PubMed, EBSCO, clinicaltrials.gov, ICTRP, and other websites, were searched for RCTs. Eleven RCTs with 1098 participants (treatment group, $n = 606$; control group, $n = 492$) were selected based on our inclusion/exclusion criteria. Two independent assessors extracted the data and performed quality assessments. The data from all eligible studies were plotted for death, major adverse cardiac events (MACE), left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), and 6-minute walk distance (6-MWD) as safety, efficacy, and performance parameters. For dose-escalation assessment, studies were categorized as low-dose (< 100 million cells) or high-dose (≥ 100 million cells).

Results MSC-based treatment is safe across low and high doses, with nonsignificant effects. However, low-dose treatment had a more significant protective effect than high-dose treatment. Subgroup analysis revealed the superiority of low-dose treatment in improving LVEF by 3.01% (95% CI; 0.65–5.38%) compared with high-dose treatment (-0.48%; 95% CI; -2.14-1.18). MSC treatment significantly improved the 6-MWD by 26.74 m (95% CI; 3.74–49.74 m) in the low-dose treatment group and by 36.73 m (95% CI; 6.74–66.72 m) in the high-dose treatment group. The exclusion of studies using ADRCs resulted in better safety and a significant improvement in LVEF from low- and high-dose MSC treatment.

Conclusion Low-dose MSC treatment was safe and superior to high-dose treatment in restoring efficacy and functional outcomes in heart failure patients, and further analysis in a larger patient group is warranted.

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Introduction

The prevalence of heart failure (HF) among adults in developed countries is approximately 1–2%, which significantly increases morbidity and mortality in addition to imposing a significant financial burden on the healthcare system [1]. The gravity of the problem may further be gauged from the figures, which show that the lifetime risk of HF has increased to 24%; every one in four persons is at risk of developing HF in their lifetime. Although different emerging therapies, including pharmacological and surgical options, have enhanced the survival rate, patients with HF still have significant mortality and hospitalization rates [2].

HF is characterized by the loss of a critical number of functioning cardiomyocytes (CMs), leading to left ventricular pump function deterioration. Given the inept intrinsic repair process, in addition to the limited potential of CMs to re-enter the cell cycle, dead CMs are replaced with noncontractile scar tissue, which throws the heart into a vicious remodeling cycle [4, 5]. Therefore, developing a therapeutic strategy for myocardial repair and regeneration remains one of the most critical research areas for HF therapy from a clinical perspective. Cell-based therapy, mainly using mesenchymal stem cells (MSCs), has shown promise in clinical trials and has moved to advanced assessment phases [6].

Mesodermal in origin, MSCs can be obtained from diverse tissue sources [7]. They are easy to isolate and propagate in vitro and exhibit superior cell biology, with minimal immunogenicity and excellent immunomodulatory properties [8]. In response to well-defined cues, these cells can differentiate into several types. One of the critical features of MSCs is their paracrine activity, releasing both soluble and insoluble factors in their microenvironment and promoting angiogenic and tissue repair by involving the intrinsic pool of stem/progenitor cells [9, 10]. Given their robust nature, they are physically or genetically manipulated to accentuate their repairability [11, 12]. During cardiovascular applications, they have been shown to protect the myocardium via multifactorial mechanisms involving anti-inflammatory activity, cardiomyogenic differentiation in and around infarct regions, angiogenesis, cytoprotection, and antifibrotic activity [13].

To date, no agreement exists regarding the relationship between the number of injected cells and the response regarding safety and efficacy. As the domain of cell-based therapy for cardiac regeneration continues to broaden and with the emergence of MSCs as candidates for living biodrugs, there is an urgent need to establish a dose-response relationship to determine an optimal dose for the required prognosis. The last two decades of clinical research have focused primarily on selecting the most suitable cell type [14–17]. Only a few dose-escalation studies have been reported to establish a dose-response relationship, but there are significant discrepancies in their design and findings [17–19]. While some research suggests that a lower cell dose is more effective, others have reported a direct or nonlinear relationship [20]. A recent meta-analysis of preclinical studies using MSC therapy for acute kidney injury reported no significant difference between cell doses [21]. Similarly, a meta-analysis of adipose-derived MSCs for the treatment of knee osteoarthritis reported no differences in safety or efficacy across high, moderate, and low doses. However, the rate of adverse events increases with increasing dose [22]. Subanalyses of clinical trials in which different cell doses were tested failed to predict or determine a relationship between dosage and response [23, 24]. These discrepancies and conflicting findings lead to the conclusion that the dose-response relationship might vary according to cell type, route of administration, disease, and source, among other factors, which poses a significant challenge.

Our meta-analysis was restricted to MSC-based phase II/III randomized controlled trials (RCTs) involving HF patients with reduced ejection fraction (HFrEF) only to avoid heterogeneity in the reported data between phase-I and RCTs, aiming to establish a dose-response relationship. We hypothesize that increasing the cell dose is safe and improves functional outcomes in HF patients. We followed the PRISMA guidelines for systematic reviews and meta-analyses to explore safety, efficacy, and functional clinical outcomes (i.e., death and MACEs, LVEF, LVESV, and the 6-MWD).

Methodology

Protocol and registration

This systemic review and meta-analysis follow the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [25] and carries the PROSPERO identification number CRD42024501959 (registered before conducting formal research or analysis).

Literature search and study selection process

A systematic literature search of PubMed, EBSCO, ICTRP, and clinicaltrials.gov was conducted between October and December 2023. The search strategy used Medical Subject Headings (MeSH) or text search fields. In EBSCO, ICTRP, and clinicaltrials.gov, we used the

search terms "heart failure," "congestive heart failure," "mesenchymal stem cells," and "mesenchymal precursor cells" in the text words with appropriate use of the Boolean operator. The search terms for PubMed included "heart failure OR congestive heart disease" AND "bone marrow mesenchymal stem cells OR bone marrow mesenchymal precursor cells." All the references of eligible studies were screened and reviewed carefully for any potential RCTs.

Inclusion and exclusion criteria
The inclusion criteria for this study were [1] a phase II/III randomized clinical trial [2], treatment using MSCs, and [3] HF patients only. The exclusion criteria were trials without a clear statement about the number of cells administered to the intervention group, treatment with other forms of intervention (e.g., CABG, different forms of stem cells, left ventricular assist device), preserved LVEF (pLVEF), and phase I trials irrespective of the cell type used.

Data extraction and outcomes of interest
Two authors checked the eligibility of the studies and extracted the data into standardized Excel spreadsheets containing several relevant variables. The primary variables included intervention, cell dose, cell sampling site, country of trial origin, etiology, sample size, sex, age, cell delivery route, imaging modality, and follow-up period. In addition, the baseline, follow-up, and mean difference, along with the standard deviation, were recorded at the last follow-up for the LVEF, LVESV, and 6MWD. The number of deaths and MACEs were recorded during the last follow-up. The study's corresponding author was approached for any missing data. However, if the corresponding author did not respond, WebPlotDigitizer was used to extract the missing values [26]. Subsequently, studies and controlled study arms with a mean dose of <100 million and ≥100 million cells were assigned to the low-dose and high-dose subgroups, respectively.

Quality assessment
The quality of the included RCTs was evaluated using the Jadad scale in three domains [27]. First, the study was awarded one point for randomization, and an additional point was awarded if the trial mentioned an appropriate randomization 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. However, one point was deducted if the blinding process was inappropriate. Finally, the third domain was the description of withdrawal or dropout during the

clinical trial process, for which the trial was awarded a point dropout. Upon completion of the evaluation process, the scores ranging from zero to five were added to determine the quality score for each trial. A trial scoring 0–2 was considered of low quality, while those scoring three or more were deemed superior.

Data synthesis and statistical analysis
Our comprehensive meta-analysis delved into clinical trials examining the dose-response effects of MSCs in treating HF patients. The study employed the LVEF, LVESV, and 6-MWD to assess the clinical effectiveness of treatment. For safety assessment, the rate of death and MACE during clinical trials were used to provide critical 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, and the 6MWD. At the same time, the risk ratio (RR) was used to compare the safety of the treatments to that of the controls. A subgroup analysis assessed the dose-response relationship and determined dose-related efficacy and safety. The significance of the results was determined using the 95% confidence interval (CI), with studies whose CI crossed the null effect line (i.e., zero) considered nonsignificant. The I-square value was used to determine between-study heterogeneity. An I-square value of <25% indicates low heterogeneity, between 25% and 75% indicates moderate heterogeneity, while values >75% indicate 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). The study by Perin et al. was a dose-escalation trial and included three arms with different doses that were all controlled. Two of the three arms were independently assigned to the low-dose subgroup, while one was assigned to the high-dose subgroup.

Based on the quality of the included studies, a sensitivity analysis excluding low-quality studies was conducted to reassess overall and subgroup effects, as low-quality studies tend to overestimate the effect size. Additionally, studies using adipose-derived regenerative cells (ADRCs) have consistently reported no benefit. Accordingly, a sensitivity analysis of LVEF and LVESV, excluding studies using ADRCs, was conducted to assess overall and subgroup effects. An additional subgroup analysis comparing studies using ADRCs and BM-MSCs was completed, comparing the impact of cell sources in both low-dose and high-dose subgroups. The analysis was performed using the SPSS version 28 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Literature review results

The four databases yielded 593 results. Most records were retrieved from EMBASE ($n=335$), followed by PubMed ($n=197$), ClinicalTrials.gov ($n=96$), and the ICTRP ($n=59$). The 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 nonhuman trials ($n=114$) were excluded. A total of 26 potential candidate trials were retrieved, excluding one. The 25 retrieved trials were then screened with our inclusion/exclusion criteria, from which crossover trials ($n=2$), noncontrolled trials ($n=3$), trials with additional intervention ($n=7$), trials with no identified dosage ($n=1$), phase I trials ($n=2$), and non-English records ($n=1$) were excluded. Two additional trials were identified through reference searching of eligible records. Subsequently, a final total of 11 trials were included in our review for analysis (Fig. 1).

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

Table 1 summarizes the salient features of the eleven trials in the systematic review and meta-analysis. The ATHENA trial consists of two parallel prospective trials. Of the eleven selected trials, five used a low dose, while the remaining six used a high dose of MSCs per our defined criterion of dose classification. Concerning autologous and allogenic cell sources, the trials used MSCs from bone marrow ($n=7$), umbilical cord ($n=1$), and adipose tissue ($n=3$). All the trials were placebo-controlled or sham-controlled, except for Perin et al. 2015, which used a mock injection technique [28]. The total number of patients in the 11 included RCTs was 1098, with 606 patients in the intervention group and 492 patients in the control group, for an approximate ratio of 1.2:1. Male participants dominated the sample ($n=869$). 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. Most trials reported

Identification of studies via databases, registers and other methods

Identification
- Records identified (n = 593):
  - Databases (n = 2)
  - Registers (n = 2)
- Records removed *before screening*:
  - Duplicates (n = 132)
  - Records marked as ineligible by filters (n = 140)
- Records identified, retrieved and assessed from:
  - Citation searching (n = 2)

Screening
- Records screened (n = 321)
  - Records excluded:
    - Irrelevant abstracts (n = 181)
    - Non-human trials (n = 114)
- Reports sought for retrieval (n = 26)
  - Reports not retrieved (n = 1)
- Reports assessed for eligibility (n = 25)
  - Reports excluded:
    - Cross-over studies (n = 2)
    - Non-controlled studies (n = 3)
    - Additional interventions or preconditioning (n = 7)
    - No identified dosage (n = 1)
    - Phase I trials (n = 2)
    - Non-English (n = 1)

Included
- Records of included studies (n = 11)
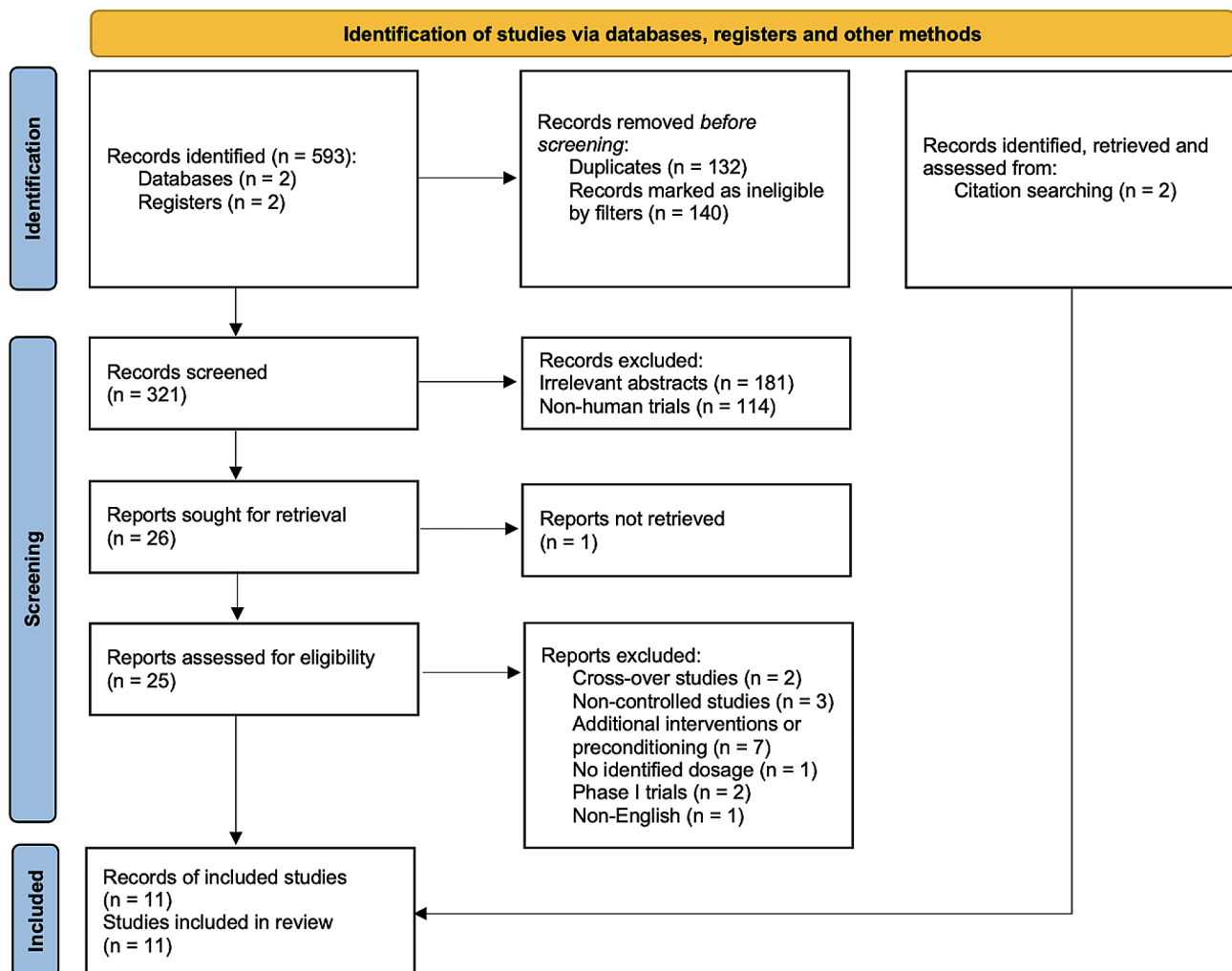- Studies included in review (n = 11)

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

Table 1 Description and characteristics of the included RCTs

Study	Arm	Dose (cells in millions)	Sampling site	Country	Etiology	Sample size	Males	Age	RoA	Imaging modality	F/U (mo)
MSC-HFT [29]	Intervention	77.5	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)			
Butler et al. [30]	Intervention	1.5/kg	Bone marrow	USA	Nonischemic Cardiomyopathy	12	13	47.3 (12.8)	IV	MRI	3
	Control					12					
Perin et al. [28]	Intervention	25/75/150	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)			
Athena Trials [31]	Intervention	40 and 80	Abdominal adipose tissue	USA	Ischemic Cardiomyopathy	17	16	64.1 (8.2)	IM	Echo	6
	Control					14	13	65.7 (7.3)			
RIMECARD Trial [32]	Intervention	1/kg	Umbilical cord	Chile	Ischemic or Nonischemic Cardiomyopathy	15	12	57.33 (10.05)	IV	Echo	12
	Control					15	14	57.20 (11.64)			
CONCERT-HF [33]	Intervention	150	Bone marrow	USA	Ischemic Cardiomyopathy	29	27	61.7 (6.7)	TE	MRI	12
	Control					32	31	63.1 (8.8)			
Danish phase II [34]	Intervention	100	Abdominal adipose tissue	Denmark	Ischemic HF	54	44	67.0 (9.0)	IM	Echo	6/12
	Control					27	24	66.6 (8.1)			
Xiao et al. [35]	Intervention	490	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 [36]	Intervention	100 or 200	Bone marrow (Iliac crest)	USA	Ischemic Cardiomyopathy	22	18	57.1 (10.6)	TE	MRI or CT	12
	Control					22	10	60 (12.0)			
SCIENCE [37]	Intervention	110	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 [38]	Intervention	150	Bone marrow	Canada, USA	Ischemic or Nonischemic HF	265	222	62.7 (10.9)	TE	Echo	12
	Control					272	221	62.6 (10.4)			

Abbreviations: Echo: Echocardiography; F/U: Follow-up; HF: Heart failure; IC: Intracoronary injection; IM: Intramyocardial injection; IV: Intravenous injection; Mo: Months; TE: RoA: Route of administration; Transendocardial injection

mean doses ranging from 25 million to 80 million cells in the low-dose group and from 100 million to 200 million cells in the high-dose group. Two RCTs reported the cell dose as cells/kg (1 million/kg and 1.5 million/kg). The follow-up period varied between the trials, with some reaching four years for safety assessment; however, 3 to 12 months were assessed to reduce heterogeneity. Most trials assessed LVEF using echocardiography (*n*=7), while others used cardiac CT or MRI (*n*=4). Transendocardial (*n*=4) and intramyocardial (*n*=4) routes were the standard modes of cell delivery, followed by intravenous (*n*=2) and intracoronary (*n*=1) routes.

Quality Assessment (risk of Bias) using the Jadad score

The Jadad score for the trials ranged between 2 and 5. Interestingly, all trials were of high quality (i.e., ≥3), except for the study by Xiao et al., which scored 2. Accordingly, the study was excluded from the primary meta-analysis to avoid effect overestimation. A detailed assessment of the included trials is shown in Table 2.

Meta-analysis for Safety and Efficacy parameters
Death and major adverse cardiac events

All the RCTs included in the review reported both death and MACE consistently. The overall RRs for death were 0.92 (95% CI; 0.50–1.71) and 0.70 (95% CI; 0.24–2.03) for the low-dose subgroup and 1.06 (95% CI; 0.50–2.26) for the high-dose subgroup (Fig. 2). The studies were homogenous, with an $I^2=0.00$. A funnel plot and Egger's regression (*p*=0.567) showed a low risk of publication bias (Supplementary Fig. 1). For MACE, the pooled RR of MACE after MSC treatment for both high- and low-dose studies was 1.01 (95% CI; 0.85–1.19). Subgroup analysis revealed RRs of 0.93 (95% CI; 0.59–1.47) for the low-dose group and 1.02 (95% CI; 0.85–1.23) for the high-dose group. The studies were highly homogenous, with an $I^2=0.00$ (Fig. 3). A funnel plot and Egger's regression (*p*=0.793) showed a low risk of publication bias (Supplementary Fig. 2). The sensitivity analysis, excluding trials using ADRCs, showed an RR of 0.84 (95% CI; 0.51–1.39) for the low-dose group, which was insignificant (Fig. 4).

Table 2 The Jadad score for risk of bias (quality) assessment

Jadad Scale for Risk of Bias Assessment

	Jadad Scale Items						
Study	J1	J2	J3	J4	J5	Total	Quality
MSC-HFT	1	1	1	1	0	4	High
Butler et al.	1	1	0	0	1	3	High
Perin et al.	1	1	1	1	1	5	High
Athena	1	0	1	1	1	4	High
RIMECARD	1	1	1	1	0	4	High
CONCERT-HF	1	1	1	1	1	5	High
Danish Phase II	1	1	1	1	0	4	High
Xiao et al.	1	1	0	0	0	2	Low
TAC-HFT	1	1	1	1	0	4	High
SCIENCE	1	1	1	1	1	5	High
DREAM-HF	1	0	1	1	1	4	High


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                                              0.922079
Dose      ID                RR   Lower Upper
High      CONCERT-HF        0.83  0.20  3.39
          Danish Phase II   3.56  0.19 66.61
          Perin et al. (arm 3) 0.14 0.01 2.55
          SCIENCE           0.72  0.12  4.13
          DREAM-HF          1.79  0.53  6.04
          Subgroup Overall  1.06  0.50  2.26

Low       MSC-HFT           0.50  0.03  7.59
          Perin et al. (arm 1) 0.14 0.01 2.55
          Perin et al. (arm 2) 0.67 0.13 3.44
          Athena            4.17  0.22 80.25
          RIMECARD          1.00  0.07 14.55
          Subgroup Overall  0.70  0.24  2.03

Overall                     0.92  0.50  1.71

              0          1          10         100
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Heterogeneity: I-squared = 0.00
Homogeneity: Q = 6.63, p-value = 0.68
Test of between-subgroup homogeneity: Q = 0.39, p-value = 0.53
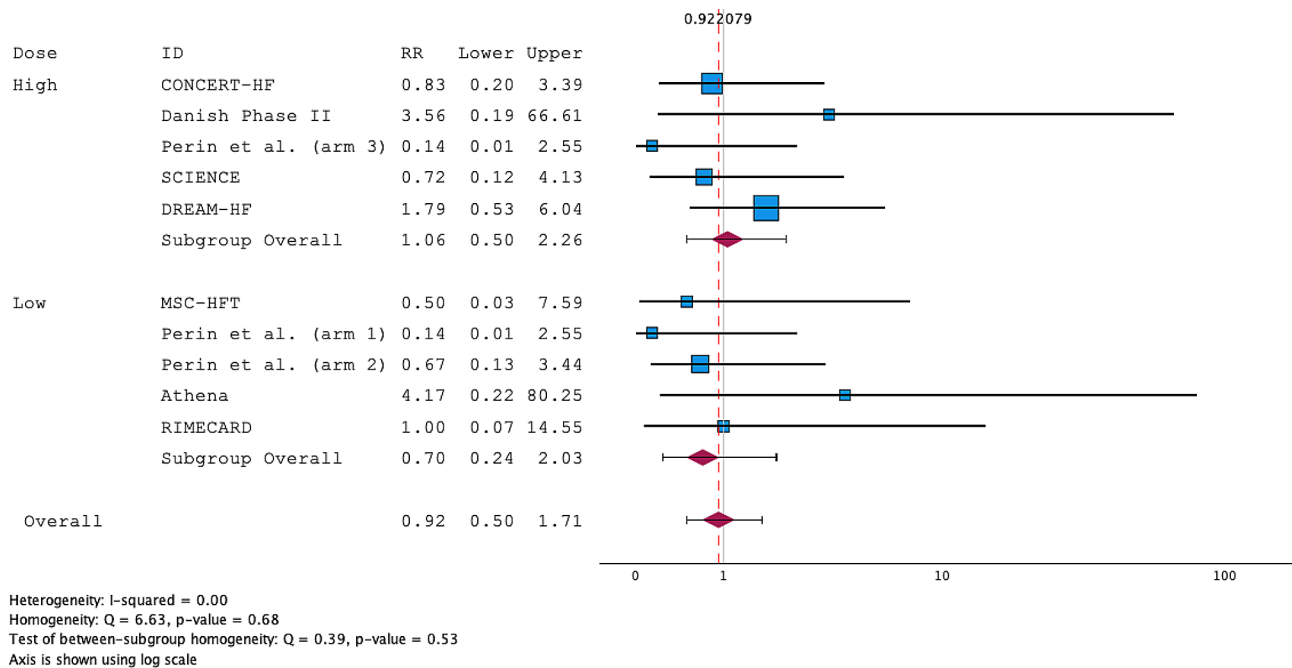Axis is shown using log scale

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

Left ventricular ejection fraction

All the included RCTs reported LVEF and its change from baseline to the follow-up period. Overall, MSC treatment improved the LVEF by 1.19% (95% CI; -0.48-2.85%) compared to the controls, with high heterogeneity (I^2=89). A funnel plot and Egger's regression showed a low risk of publication bias (p=0.507), with consistent subgroup findings (Supplementary Fig. 3). Subgroup analysis revealed a significant improvement of 3.01% (95% CI; 0.65–5.38%) with low-dose treatment vs. controls and a nonsignificant deterioration of -0.48% (95% CI; -2.14-1.18) with high-dose treatment (Fig. 5).

Interestingly, a sensitivity analysis excluding the ADRC trials showed remarkable improvements in LVEF across both doses (Fig. 6). Further subgroup analysis comparing ADRCs with BMMSCs revealed that ADRCs had a significantly inferior effect (see Supplementary Fig. 4 and Supplementary Fig. 5). Analysis of the LVESV revealed no significant changes across the two dose categories (Supplementary Fig. 6).

6-Minute Walk Distance

Only four of the included RCTs, with six arms, reported changes from baseline to the follow-up period. The RIMECARD, Athena, and DREAM-HF trials did not use the 6MWD as an endpoint. The remaining trials measured the distance at baseline and follow-up but did not report the change. The corresponding authors were contacted multiple times to provide the necessary data for the analysis and have yet to respond. Overall, MSC
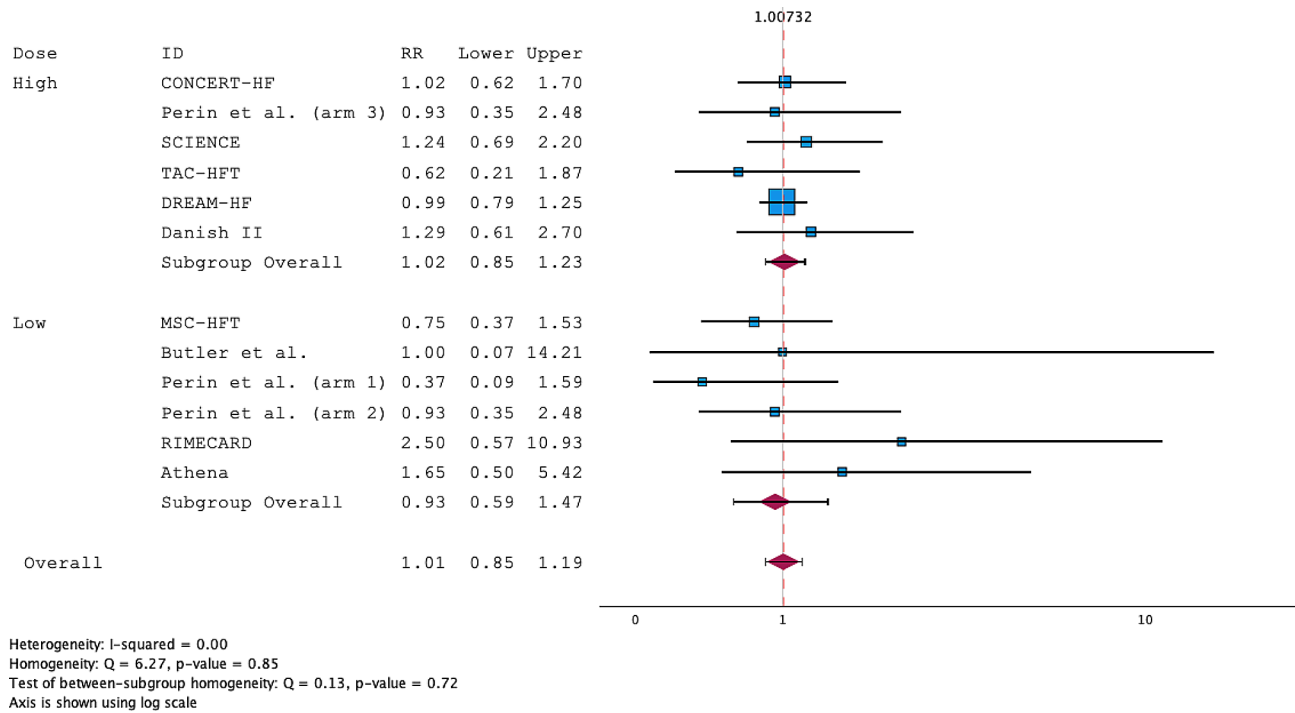
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                                              1.00732
Dose       ID                 RR    Lower Upper
High       CONCERT-HF         1.02  0.62  1.70
           Perin et al. (arm 3) 0.93  0.35  2.48
           SCIENCE            1.24  0.69  2.20
           TAC-HFT            0.62  0.21  1.87
           DREAM-HF           0.99  0.79  1.25
           Danish II          1.29  0.61  2.70
           Subgroup Overall   1.02  0.85  1.23

Low        MSC-HFT            0.75  0.37  1.53
           Butler et al.      1.00  0.07  14.21
           Perin et al. (arm 1) 0.37  0.09  1.59
           Perin et al. (arm 2) 0.93  0.35  2.48
           RIMECARD           2.50  0.57  10.93
           Athena             1.65  0.50  5.42
           Subgroup Overall   0.93  0.59  1.47

Overall                       1.01  0.85  1.19

                          0          1              10
```

Heterogeneity: I-squared = 0.00
Homogeneity: Q = 6.27, p-value = 0.85
Test of between-subgroup homogeneity: Q = 0.13, p-value = 0.72
Axis is shown using log scale

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

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                                              0.959628
Dose       ID                 RR    Lower Upper
High       CONCERT-HF         1.02  0.62  1.70
           Perin et al. (arm 3) 0.93  0.35  2.48
           TAC-HFT            0.62  0.21  1.87
           DREAM-HF           0.99  0.79  1.25
           Subgroup Overall   0.98  0.80  1.20

Low        MSC-HFT            0.75  0.37  1.53
           Butler et al.      1.00  0.07  14.21
           Perin et al. (arm 1) 0.37  0.09  1.59
           Perin et al. (arm 2) 0.93  0.35  2.48
           RIMECARD           2.50  0.57  10.93
           Subgroup Overall   0.84  0.51  1.39

Overall                       0.96  0.80  1.16

                          0          1              10
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Heterogeneity: I-squared = 0.00
Homogeneity: Q = 4.45, p-value = 0.81
Test of between-subgroup homogeneity: Q = 0.29, p-value = 0.59
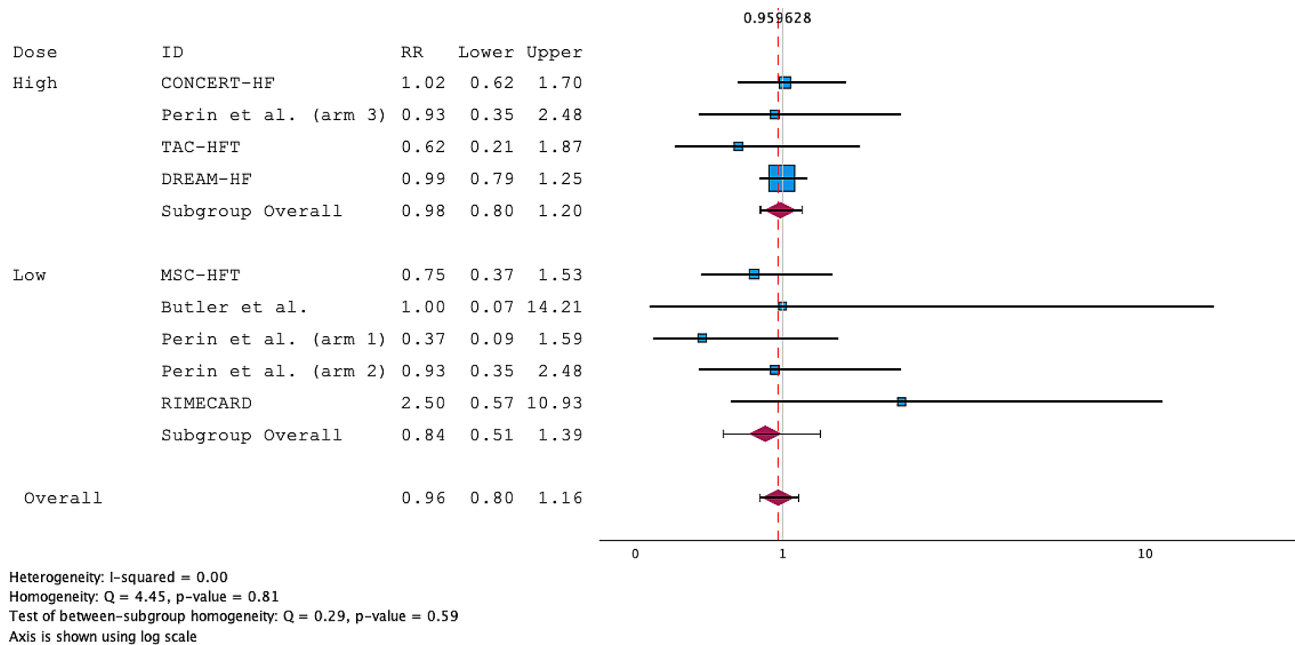Axis is shown using log scale

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

treatment increased the 6MWD by 29.61 m (95% CI; 13.57–44.65 m), with low heterogeneity ($I^2=0.00$) (Fig. 7). A funnel plot and Egger's regression showed a low risk of publication bias ($p=0.789$). , with consistent subgroup findings (Supplementary Fig. 7). Subgroup analysis revealed a significant increase in the 6-MWD compared with that of controls (26.74 m; 95% CI; 3.74–49.74 m) with low-dose treatment and 36.73 m (95% CI; 6.74–66.72 m) with high-dose treatment (Fig. 7).

Discussion

Our systematic review and meta-analysis of eleven RCTs was aimed to establish a dose-response relationship between the safety and efficacy parameters of MSC-based
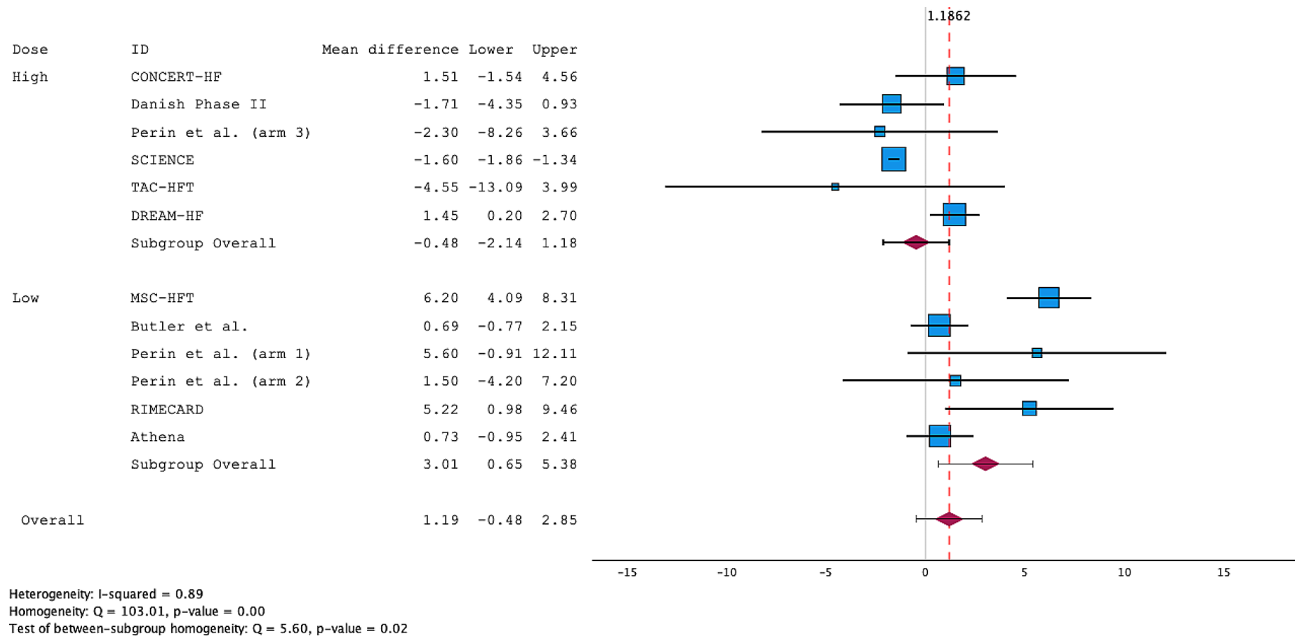
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                                                                          1.1862
Dose        ID                  Mean difference Lower  Upper
High        CONCERT-HF                     1.51  -1.54   4.56
            Danish Phase II               -1.71  -4.35   0.93
            Perin et al. (arm 3)          -2.30  -8.26   3.66
            SCIENCE                       -1.60  -1.86  -1.34
            TAC-HFT                       -4.55 -13.09   3.99
            DREAM-HF                       1.45   0.20   2.70
            Subgroup Overall              -0.48  -2.14   1.18

Low         MSC-HFT                        6.20   4.09   8.31
            Butler et al.                  0.69  -0.77   2.15
            Perin et al. (arm 1)           5.60  -0.91  12.11
            Perin et al. (arm 2)           1.50  -4.20   7.20
            RIMECARD                       5.22   0.98   9.46
            Athena                         0.73  -0.95   2.41
            Subgroup Overall               3.01   0.65   5.38

Overall                                    1.19  -0.48   2.85

                                 -15   -10   -5    0    5    10    15
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Heterogeneity: I-squared = 0.89
Homogeneity: Q = 103.01, p-value = 0.00
Test of between-subgroup homogeneity: Q = 5.60, p-value = 0.02

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

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                                                                          2.22637
Dose        ID                  Mean difference Lower  Upper
High        CONCERT-HF                     1.51  -1.54   4.56
            Perin et al. (arm 3)          -2.30  -8.26   3.66
            TAC-HFT                       -4.55 -13.09   3.99
            DREAM-HF                       1.45   0.20   2.70
            Subgroup Overall               1.22   0.08   2.35

Low         MSC-HFT                        6.20   4.09   8.31
            Butler et al.                  0.69  -0.77   2.15
            Perin et al. (arm 1)           5.60  -0.91  12.11
            Perin et al. (arm 2)           1.50  -4.20   7.20
            RIMECARD                       5.22   0.98   9.46
            Subgroup Overall               3.68   0.97   6.39

Overall                                    2.23   0.32   4.14

                                 -15   -10   -5    0    5    10    15
```

Heterogeneity: I-squared = 0.72
Homogeneity: Q = 26.79, p-value = 0.00
Test of between-subgroup homogeneity: Q = 2.70, p-value = 0.10
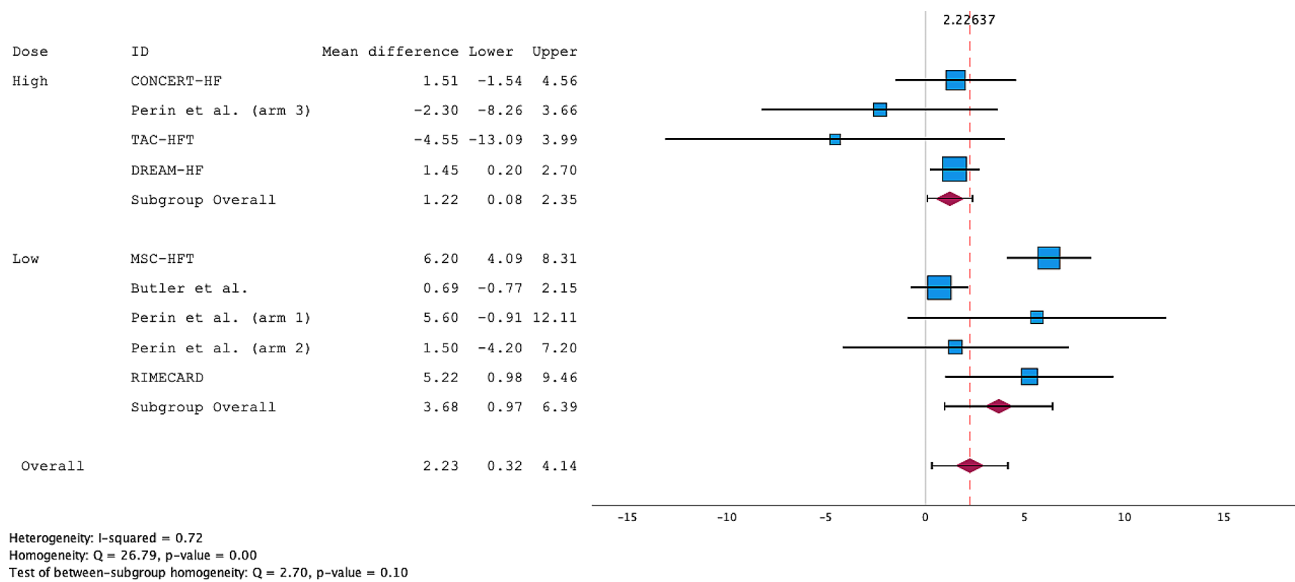
Fig. 6 Forest plot of the weighted mean difference (WMD) for LVEF meta-analysis excluding ADRC trials

therapy in HFrEF patients. MSCs are rapidly emerging as the cells of choice in regenerative medicine for use as living biodrugs. The main findings of our meta-analysis include the following: (1) All but one of the eleven trials included in the meta-analysis scored high on the Jadad scale, (2) Low-dose MSC treatment was safer and more effective than high-dose MSC treatment in improving efficacy and functional parameters. (3) There was no consensus on defining a low or a high dose in the published RCTs; and (4) BM-derived MSCs were more efficacious than either AD- or UC-derived MSCs.

Different mechanisms contribute to heart failure with preserved ejection fraction (HFpEF) than to HFrEF, and the mechanisms by which cell therapy drives its effects under both conditions seem to differ; therefore, we limited our analysis to the population with HFrEF [39, 40]. We only included MSC injection as the sole treatment to eliminate confounding effects from other interventions. The analysis indicated that low—and high-dose MSC treatments are safe in terms of death and MACE occurrence. Moreover, the results obtained from the sensitivity analysis showed a tendency toward protective effects
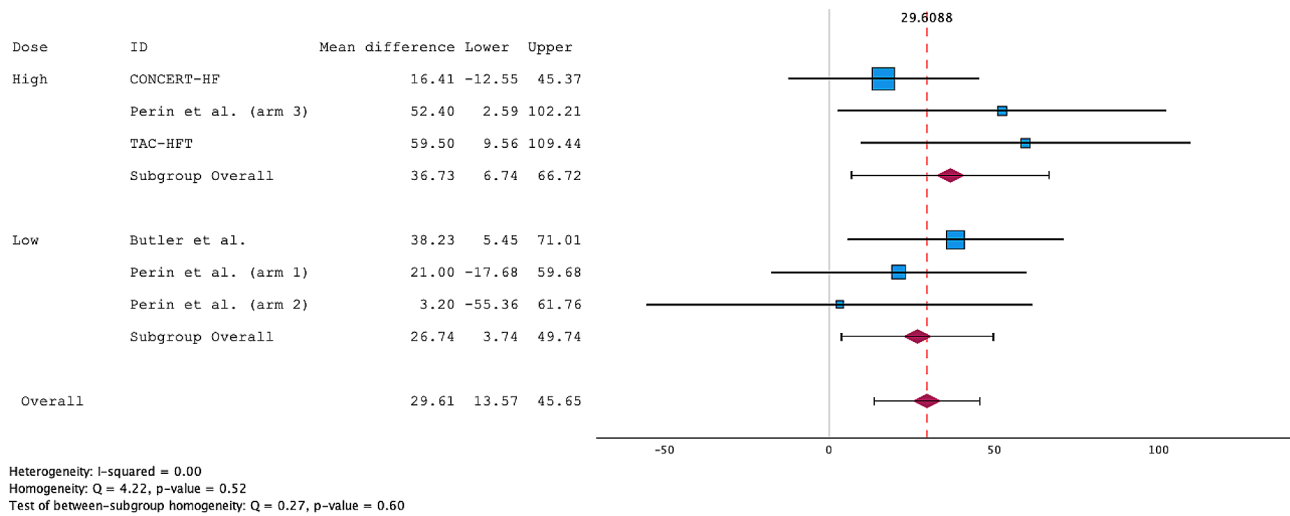
```
Dose       ID              Mean difference Lower  Upper
High       CONCERT-HF               16.41 -12.55  45.37
           Perin et al. (arm 3)     52.40   2.59 102.21
           TAC-HFT                  59.50   9.56 109.44
           Subgroup Overall         36.73   6.74  66.72

Low        Butler et al.            38.23   5.45  71.01
           Perin et al. (arm 1)     21.00 -17.68  59.68
           Perin et al. (arm 2)      3.20 -55.36  61.76
           Subgroup Overall         26.74   3.74  49.74

Overall                             29.61  13.57  45.65
```

Heterogeneity: I–squared = 0.00
Homogeneity: Q = 4.22, p–value = 0.52
Test of between–subgroup homogeneity: Q = 0.27, p–value = 0.60

Fig. 7 Forest plot of the weighted mean difference (WMD) for the 6MWD meta-analysis

with low-dose MSC treatment. MSC safety in heart disease and heart failure has been well documented in trials and studies investigating safety in greater depth. Hence, we only analyzed the occurrence of MACE [6, 41–43].

Despite extensive research on MSCs in preclinical and clinical studies, more effort must be made to establish a cell dose-response relationship and determine the optimal cell dose for the desired outcomes. Dose, besides Volume of distribution (Vd) and Clearance, is one of the primary pharmacokinetic parameters that must be defined well for all pharmaceuticals and biopharmaceuticals, including cells as living biodrugs, to achieve optimal pharmacodynamics. Hence, defining the optimal dose will ensure that the clinical use of MSC-based therapy is successful. Their innate heterogeneity and multifarious mechanism of action, which entail several intricate inter- and intracellular pathways, will continue to obscure a clear dose-response relationship for MSCs until well-defined and well-designed dose-escalation studies are performed as a concerted effort between research groups involved therein to ensure that low, moderate and high doses are well-defined. The currently reported contradictory data about the relationship between cell dose and clinical outcomes may be attributed to the inconsistent and diverse classification of low, moderate, and high doses. Given the lack of a consensus on defining cell dose in the published RCTs, our arbitrary classification of low and high cell doses is based on our observations of the doses used during these RCTs in HF patients to facilitate our meta-analysis.

The dose-response efficacy analysis revealed an inverse relationship, as evidenced by improvements in the LVEF and LVESV. However, only five of the included RCTs reported changes in the 6-MWD, which included three arms in the high-dose subgroup and only two in the low-dose subgroup. Consequently, despite being encouraging,

the results from the 6-MWD suffer from apparent data deficiency and require cautious interpretation. Preclinical studies support the inverse dosage response, as exceeding particular dosing thresholds can affect cell retention, survival, and function [44, 45]. Our results align with the PROMETHEUS and POSEIDON trials, as both used MSCs in HFrEF. The POSEIDON trial demonstrated that cell therapy had an inverse dose-response relationship with LVEF improvements. It was reported that 20 million cells had a more significant effect than 200 million cells, which could not be attributed to differences in baseline values. Similarly, the PROMETHEUS trial revealed substantial increases in LVEF in the low-dose (20 million cells) group compared to the high-dose (200 million cells) group. Some trials using cells other than MSCs support the inverse dose-response relationship [46, 47].

Some trials also support a direct dose-response relationship [19, 48]. For example, with 20 million and 100 million cells at low and high doses, respectively, the TRIDENT trial reported significant LVEF improvement only in patients treated with 100 million cells, indicating a direct dose-response relationship [48]. As we used 100 million cells as a low-dose treatment in our meta-analysis, there is a possibility that there is an upper limit for the cell dose beyond which the direct dose-response relationship changes into an inverse dose-response relationship. In addition to cell number, cell concentration may also affect the response. Higher cell concentrations may result in higher viscosity, leading to sedimentation, uneven injection flow, and cell death due to limited oxygen diffusion and increased shear forces [49, 50]. It is thus suggested that increasing the dose is beneficial until a "ceiling dose" is reached, beyond which an increase in the cell dose does not add any benefits. These observations necessitate ascertaining this dose-response relationship to guide future large phase III trials.

ADRCs are considered better candidates for therapeutic applications than their counterparts from other tissue sources due to their ease of availability in large quantities. Additionally, adipose tissue is more abundant and accessible to collect with lower invasiveness. However, using one cell population over another may benefit patients with specific pathologies [51–53]. Several clinical and preclinical studies have reported the superiority of ADRCs [54, 55]. However, there is limited cardiomyogenic differentiation [56, 57]. However, akin to BM-MSCs, paracrine effects lead to proangiogenic, antiapoptotic, and immunomodulatory effects [58–61]. Although animal studies using ADRCs were very promising and showed significant improvements in cardiac function [62], phase I studies in patients with heart failure generally showed no significant improvements in cardiac functional parameters. However, they are safe [63, 64]. Our findings indicate that BM-MSCs might be superior to ADRCs in terms of efficacy in HFrEF patients. Nevertheless, these findings should be confirmed with further, more extensive phase II/III studies primarily focusing on cell dose gradation and dose escalation to develop a dose-response relationship for fast-emerging MSCs as living biodrugs.

Despite encouraging safety and efficacy data leading to improved functional outcomes regarding the 6-MWD, the study has limitations. For example, inconsistencies in reporting functional parameters such as the 6-MWD and New York Heart Association (NYHA) class data during the follow-up period made it difficult to assess these parameters accurately. Additionally, the study did not include multiple trials that examined the dose-response effect by following a dose escalation protocol, mainly due to the lack of a control arm. Moreover, heterogeneity in clinical design, such as the route of administration, source, sampling site, and follow-up period, may affect the reliability of and bias the results. However, the study results provide preliminary insight into the dose-response relationship to guide the future design of clinical trials.

Conclusions

In conclusion, our results support low-dose MSC treatment in HFrEF patients for improved safety and efficacy. Including phase II/III RCTs involving HFrEF patients treated with MSC-based therapy reduced the risk of bias. Our data provide insight into determining the appropriate dosage before proceeding with large phase III trials. Subgroup analysis suggested the superiority of BM-derived MSCs over ADSCs. Nevertheless, these data warrant further investigation to establish a dose-response relationship using well-defined categorization of low, medium, and high doses of cells.

Abbreviations
CMs	Cardiomyocytes
HF	Heart failure
HFrEF	HF patients with reduced ejection fraction
LVEF	Left ventricular ejection fraction
LVESV	Left ventricular end-systolic volume
MACE	Major adverse cardiac events
MSCs	Mesenchymal stem cells
6-MWD	6-Minute walk distance
RCTs	Randomized controlled trials

Supplementary Information
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Supplementary Material 1

Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethics approval and consent to participate were not applicable, and this was a systematic review and meta-analysis of the published data

Consent for publication
All authors have consented to publish the paper in SCRT.

Competing interests
None of the authors have any competing interests

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References

1. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart Disease and Stroke Statistics—2022 update: a Report from the American Heart Association. Circulation. 2022;145(8):e153–639.
2. Bozkurt B, Ahmad T, Alexander KM, Baker WL, Bosak K, Breathett K, et al. Heart failure epidemiology and outcomes statistics: a report of the Heart Failure Society of America. J Card Fail. 2023;29(10):1412–51.
3. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovasc Pathol. 2012;21(5):365–71.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2016;18(8):891–975.
5. Bayeva M, Sawicki KT, Butler J, Gheorghiade M, Ardehali H. Molecular and Cellular basis of viable dysfunctional myocardium. Circulation: Heart Fail. 2014;7(4):680–91.
6. Kalou Y, Al-Khani AM, Haider KH. Bone marrow mesenchymal stem cells for heart failure treatment: a systematic review and Meta-analysis. Heart Lung Circ. 2023;32(7):870–80.
7. Kamal M, Kassem D, Haider KH. Sources and therapeutic strategies of mesenchymal stem cells in Regenerative Medicine. In: Haider KH, editor. Handbook of Stem Cell Therapy. Singapore: Springer Singapore; 2022. pp. 1–28.
8. Alvarez-Viejo M, Haider KH. Mesenchymal stem cells. In: Haider KH, editor. Handbook of Stem Cell Therapy. Singapore: Springer Singapore; 2022. pp. 1–37.
9. Haider HK, Jiang S, Idris NM, Ashraf M. IGF-1–Overexpressing mesenchymal stem cells accelerate bone marrow stem cell mobilization via paracrine activation of SDF-1α/CXCR4 signaling to promote myocardial repair. Circul Res. 2008;103(11):1300–8.
10. Chang C, Yan J, Yao Z, Zhang C, Li X, Mao HQ. Effects of mesenchymal stem cell-derived paracrine signals and their delivery strategies. Adv Healthc Mater. 2021;10(7):e2001689.
11. Jiang S, Haider H, Idris NM, Salim A, Ashraf M. Supportive interaction between cell survival signaling and angiocompetent factors enhances donor cell survival and promotes angiomyogenesis for cardiac repair. Circ Res. 2006;99(7):776–84.
12. Kim HW, Jiang S, Ashraf M, Haider KH. Stem cell-based delivery of Hypoxamir-210 to the infarcted heart: implications on stem cell survival and preservation of infarcted heart function. J Mol Med (Berl). 2012;90(9):997–1010.
13. Guo Y, Yu Y, Hu S, Chen Y, Shen Z. The therapeutic potential of mesenchymal stem cells for cardiovascular diseases. Cell Death Dis. 2020;11(5):349.
14. de la Fuente LM, Stertzer SH, Argentieri J, Peñaloza E, Miano J, Koziner B, et al. Transendocardial autologous bone marrow in chronic myocardial infarction using a helical needle catheter: 1-year follow-up in an open-label, nonrandomized, single-center pilot study (the TABMMI study). Am Heart J. 2007;154(1):79.e1-.e7.
15. Perin EC, Willerson JT, Pepine CJ, Henry TD, Ellis SG, Zhao DX, et al. Effect of transendocardial delivery of autologous bone marrow mononuclear cells on functional capacity, left ventricular function, and perfusion in chronic heart failure: the FOCUS-CCTRN trial. JAMA. 2012;307(16):1717–26.
16. Williams AR, Trachtenberg B, Velazquez DL, McNiece I, Altman P, Rouy D, et al. Intramyocardial stem cell injection in patients with ischemic cardiomyopathy: functional recovery and reverse remodeling. Circ Res. 2011;108(7):792–6.
17. Losordo DW, Henry TD, Davidson C, Sup Lee J, Costa MA, Bass T, et al. Intramyocardial, autologous CD34 + cell therapy for refractory angina. Circ Res. 2011;109(4):428–36.
18. Hare JM, Fishman JE, Gerstenblith G, DiFede Velazquez DL, Zambrano JP, Suncion VY, et al. Comparison of allogeneic vs autologous bone marrow–derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial. JAMA. 2012;308(22):2369–79.
19. Quyyumi AA, Waller EK, Murrow J, Esteves F, Galt J, Oshinski J, et al. CD34(+) cell infusion after ST elevation myocardial infarction is associated with improved perfusion and is dose-dependent. Am Heart J. 2011;161(1):98–105.
20. Golpanian S, Schulman IH, Ebert RF, Heldman AW, DiFede DL, Yang PC, et al. Concise review: review and perspective of cell dosage and routes of Administration from Preclinical and Clinical studies of Stem Cell Therapy for Heart Disease. Stem Cells Transl Med. 2016;5(2):186–91.
21. Wanyan P, Wang X, Li N, Huang Y, She Y, Zhang L. Mesenchymal stem cells therapy for acute kidney injury: a systematic review with meta-analysis based on rat model. Front Pharmacol. 2023;14.
22. Huang Z, Zhang S, Cao M, Lin Z, Kong L, Wu X, et al. What is the optimal dose of adipose-derived mesenchymal stem cells treatment for knee osteoarthritis? A conventional and network meta-analysis of randomized controlled trials. Stem Cell Res Ther. 2023;14(1):245.
23. Quyyumi AA, Vasquez A, Kereiakes DJ, Klapholz M, Schaer GL, Abdel-Latif A, et al. PreSERVE-AMI: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Intracoronary Administration of Autologous CD34 + cells in patients with left ventricular dysfunction Post STEMI. Circ Res. 2017;120(2):324–31.
24. Golpanian S, DiFede DL, Khan A, Schulman IH, Landin AM, Tompkins BA, et al. Allogeneic human mesenchymal stem cell infusions for aging Frailty. J Gerontol Biol Sci Med Sci. 2017;72(11):1505–12.
25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
26. Drevon D, Fursa SR, Malcolm AL. Intercoder Reliability and Validity of WebPlotDigitizer in extracting Graphed Data. Behav Modif. 2017;41(2):323–39.
27. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1–12.
28. Perin EC, Borow KM, Silva GV, DeMaria AN, Marroquin OC, Huang PP, et al. A phase II dose-escalation study of allogeneic mesenchymal precursor cells in patients with ischemic or nonischemic heart failure. Circ Res. 2015;117(6):576–84.
29. Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Kofoed KF, Haack-Sørensen M, et al. Bone marrow-derived mesenchymal stromal cell treatment in patients with ischemic heart failure: final 4-year follow-up of the MSC-HF trial. Eur J Heart Fail. 2020;22(5):884–92.
30. Butler J, Epstein SE, Greene SJ, Quyyumi AA, Sikora S, Kim RJ, et al. Intravenous allogeneic mesenchymal stem cells for nonischemic cardiomyopathy. Circul Res. 2017;120(2):332–40.
31. Henry TD, Pepine CJ, Lambert CR, Traverse JH, Schatz R, Costa M, et al. The Athena trials: autologous adipose-derived regenerative cells for refractory chronic myocardial ischemia with left ventricular dysfunction. Catheter Cardiovasc Interv. 2017;89(2):169–77.
32. Bartolucci J, Verdugo FJ, González PL, Larrea RE, Abarzua E, Goset C, et al. Safety and Efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure. Circul Res. 2017;121(10):1192–204.
33. Bolli R, Mitrani RD, Hare JM, Pepine CJ, Perin EC, Willerson JT, et al. A phase II study of autologous mesenchymal stromal cells and c-kit positive cardiac cells, alone or in combination, in patients with ischemic heart failure: the CCTRN CONCERT-HF trial. Eur J Heart Fail. 2021;23(4):661–74.
34. Qayyum AA, Mouridsen M, Nilsson B, Gustafsson I, Schou M, Nielsen OW, et al. Danish phase II trial using adipose tissue-derived mesenchymal stromal cells for patients with ischemic heart failure. ESC Heart Fail. 2023;10(2):1170–83.
35. Xiao W, Guo S, Gao C, Dai G, Gao Y, Li M, et al. A randomized comparative study on the efficacy of Intracoronary infusion of autologous bone marrow mononuclear cells and mesenchymal stem cells in patients with dilated cardiomyopathy. Int Heart J. 2017;58(2):238–44.
36. Heldman AW, DiFede DL, Fishman JE, Zambrano JP, Trachtenberg BH, Karantalis V, et al. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. JAMA. 2014;311(1):62–73.
37. Qayyum AA, van Klarenbosch B, Frljak S, Cerar A, Poglajen G, Traxler-Weidenauer D, et al. Effect of allogeneic adipose tissue-derived mesenchymal stromal cell treatment in chronic ischemic heart failure with reduced ejection fraction - the SCIENCE trial. Eur J Heart Fail. 2023;25(4):576–87.
38. Perin EC, Borow KM, Henry TD, Mendelsohn FO, Miller LW, Swiggum E, et al. Randomized Trial of targeted transendocardial mesenchymal precursor cell therapy in patients with heart failure. J Am Coll Cardiol. 2023;81(9):849–63.
39. Domaszk O, Skwarek A, Wojciechowska M. In search of the Holy Grail: Stem Cell Therapy as a Novel Treatment of Heart failure with preserved ejection fraction. Int J Mol Sci. 2023;24(5):4903.
40. Frljak S, Poglajen G, Vrtovec B. Cell therapy in Heart failure with preserved ejection fraction. Card Fail Rev. 2022;8:e08.
41. Krishna Mohan GV, Tirumandyam G, Vemulapalli HS, Vajje J, Asif H, Saleem F. Mesenchymal stem cell therapy for a Better Prognosis of Heart Failure: a systematic review and Meta-analysis of Randomized controlled trials. Cureus. 2023;15(8):e43037.
42. Lalu MM, Mazzarello S, Zlepnig J, Dong YYR, Montroy J, McIntyre L, et al. Safety and Efficacy of Adult Stem Cell Therapy for Acute myocardial infarction and ischemic heart failure (SafeCell Heart): a systematic review and Meta-analysis. Stem Cells Transl Med. 2018;7(12):857–66.

43. Fan M, Huang Y, Chen Z, Xia Y, Chen A, Lu D, et al. Efficacy of mesenchymal stem cell therapy in systolic heart failure: a systematic review and meta-analysis. Stem Cell Res Ther. 2019;10(1):150.

44. Lee ST, White AJ, Matsushita S, Malliaras K, Steenbergen C, Zhang Y, et al. Intramyocardial injection of autologous cardiospheres or cardiosphere-derived cells preserves function and minimizes adverse ventricular remodeling in pigs with heart failure postmyocardial infarction. J Am Coll Cardiol. 2011;57(4):455–65.

45. Hamamoto H, Gorman JH 3rd, Ryan LP, Hinmon R, Martens TP, Schuster MD, et al. Allogeneic mesenchymal precursor cell therapy to limit remodeling after myocardial infarction: the effect of cell dosage. Ann Thorac Surg. 2009;87(3):794–801.

46. Bartunek J, Terzic A, Davison BA, Filippatos GS, Radovanovic S, Beleslin B, et al. Cardiopoietic cell therapy for advanced ischemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial. Eur Heart J. 2016;38(9):648–60.

47. Losordo DW, Henry TD, Davidson C, Lee JS, Costa MA, Bass T, et al. Intramyocardial, Autologous CD34 + cell therapy for refractory angina. Circul Res. 2011;109(4):428–36.

48. Florea V, Rieger AC, DiFede DL, El-Khorazaty J, Natsumeda M, Banerjee MN, et al. Dose comparison study of allogeneic mesenchymal stem cells in patients with ischemic cardiomyopathy (the TRIDENT study). Circul Res. 2017;121(11):1279–90.

49. Potts MB, Silvestrini MT, Lim DA. Devices for cell transplantation into the central nervous system: design considerations and emerging technologies. Surg Neurol Int. 2013;4(Suppl 1):S22–30.

50. Rossetti T, Nicholls F, Modo M. Intracerebral Cell Implantation: Preparation and characterization of cell suspensions. Cell Transpl. 2016;25(4):645–64.

51. Strioga M, Viswanathan S, Darinskas A, Slaby O, Michalek J. Same or not the same? Comparison of adipose tissue-derived Versus Bone Marrow-derived mesenchymal stem and stromal cells. Stem Cells Dev. 2012;21(14):2724–52.

52. El-Badawy A, Amer M, Abdelbaset R, Sherif SN, Abo-Elela M, Ghallab YH, et al. Adipose stem cells display higher regenerative capacities and more adaptable Electro-Kinetic properties compared to bone marrow-derived mesenchymal stromal cells. Sci Rep. 2016;6(1):37801.

53. Safwan M, Bourgleh MS, Alshakaki H, Molhem A, Haider KH. Morbid cell status and Donor Age significantly alter mesenchymal stem cell functionality and reparability. In: Haider KH, editor. Handbook of stem cell applications. Singapore: Springer Nature Singapore; 2023. pp. 1–29.

54. Muthu S, Patil SC, Jeyaraman N, Jeyaraman M, Gangadaran P, Rajendran RL, et al. Comparative effectiveness of adipose-derived mesenchymal stromal cells in the management of knee osteoarthritis: a meta-analysis. World J Orthop. 2023;14(1):23–41.

55. Zhou LN, Wang JC, Zilundu PLM, Wang YQ, Guo WP, Zhang SX, et al. A comparison of the use of adipose-derived and bone marrow-derived stem cells for peripheral nerve regeneration in vitro and in vivo. Stem Cell Res Ther. 2020;11(1):153.

56. Chang JC, Lee PC, Lin YC, Lee KW, Hsu SH. Primary adipose-derived stem cells enriched by growth factor treatment improves cell adaptability toward cardiovascular differentiation in a rodent model of acute myocardial infarction. J Stem Cells. 2011;6(1):21–37.

57. Mazo M, Planat-Bénard V, Abizanda G, Pelacho B, Léobon B, Gavira JJ, et al. Transplantation of adipose derived stromal cells is associated with functional improvement in a rat model of chronic myocardial infarction. Eur J Heart Fail. 2008;10(5):454–62.

58. Chen L, Qin F, Ge M, Shu Q, Xu J. Application of adipose-derived stem cells in heart disease. J Cardiovasc Transl Res. 2014;7(7):651–63.

59. Yang D, Wang W, Li L, Peng Y, Chen P, Huang H, et al. The relative contribution of paracine effect versus direct differentiation on adipose-derived stem cell transplantation mediated cardiac repair. PLoS ONE. 2013;8(3):e59020.

60. Paul A, Srivastava S, Chen G, Shum-Tim D, Prakash S. Functional Assessment of adipose stem cells for Xenotransplantation using myocardial infarction immunocompetent models: comparison with bone marrow stem cells. Cell Biochem Biophys. 2013;67(2):263–73.

61. Rasmussen JG, Frøbert O, Holst-Hansen C, Kastrup J, Baandrup U, Zachar V, et al. Comparison of human adipose-derived stem cells and bone marrow-derived stem cells in a myocardial infarction model. Cell Transpl. 2014;23(2):195–206.

62. Matsushita K. Heart failure and adipose mesenchymal stem cells. Trends Mol Med. 2020;26(4):369–79.

63. 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;168(1):88–e952.

64. Kastrup J, Haack-Sørensen M, Juhl M, Harary Søndergaard R, Follin B, Drozd Lund L, et al. Cryopreserved off-the-Shelf Allogeneic adipose-derived stromal cells for therapy in patients with ischemic heart disease and heart Failure-A Safety Study. Stem Cells Transl Med. 2017;6(11):1963–71.

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