Prevention of acute myocardial infarction induced heart failure by intracoronary infusion of mesenchymal stem cells: phase 3 randomised clinical trial (PREVENT-TAHA8)

Armin Attar,[1] Seyed Alireza Mirhosseini,[1] Anthony Mathur,[2,3,4] Sheik Dowlut,[2,3,4] Ahmad Monabati,[5,6] Mohammad Kasaei,[1] Firoozeh Abtahi,[1] Yahya Kiwan,[7] Massoud Vosough,[8] Negar Azarpira[9]

For numbered affiliations see end of the article

Correspondence to: Armin Attar attar_armin@yahoo.com; (ORCID 0000-0002-4133-4870)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;391:e083382 http://dx.doi.org/10.1136/bmj-2024-083382

Accepted: 16 August 2025

ABSTRACT

OBJECTIVE

To assess the effect of intracoronary infusion of mesenchymal stem cells on the development of post-myocardial infarction heart failure.

DESIGN

Phase 3 randomised clinical trial.

SETTING

Three tertiary hospitals in Shiraz, Iran.

PARTICIPANTS

420 patients with a first ST segment elevation acute myocardial infarction and left ventricular ejection fraction ‹40% were enrolled and randomised in a 1:2 ratio to receive intervention or standard care.

INTERVENTION

Intracoronary infusion of allogenic Wharton's jelly derived mesenchymal stem cells within 3-7 days of acute myocardial infarction in addition to standard care.

MAIN OUTCOME MEASURES

The primary endpoint was incidence of heart failure. Secondary endpoints included readmission to hospital for heart failure, all cause mortality, cardiovascular mortality, and readmission to hospital for myocardial infarction. Changes in left ventricular ejection fraction within six months post-myocardial infarction were compared between groups.

RESULTS

A total of 396 patients (136 in the intervention group and 260 in the control group) were included in the final analysis, with a median follow-up of 33.2 months. Intracoronary infusion of mesenchymal stem cells had a preventive effect for incidence of heart failure (2.77 *v* 6.48 per 100 person years; hazard ratio 0.43, 95% confidence interval 0.21 to 0.89; P=0.024), readmission to hospital for heart failure (0.92 *v* 4.20 per 100 person years; 0.22, 0.06 to 0.74; P=0.015), and a composite endpoint of cardiovascular mortality and readmission for myocardial infarction or heart failure (2.80 *v* 7.16 per 100 person years; 0.39, 0.19 to 0.82; P=0.012). The intervention did not have a statistically significant effect on readmission to hospital for myocardial infarction (1.23 *v* 3.06 per 100 person years; hazard ratio 0.40, 0.14 to 1.19; P=0.10), all cause mortality (1.81 *v* 1.66 per 100 person years; 1.10, 0.40 to 3.02; P=0.86), or cardiovascular mortality (0.91 *v* 1.33 per 100 person years; 0.68, 0.18 to 2.57; P=0.57). Left ventricular ejection fraction in the intervention group showed a significantly greater improvement from baseline at six months compared with the control group (β=5.88, 95% confidence interval 4.00 to 7.76; P‹0.001).

CONCLUSIONS

Intracoronary infusion of Wharton's jelly derived mesenchymal stem cells significantly reduced the risk of incidence of heart failure, readmission to hospital for heart failure, and the composite endpoint of cardiovascular mortality and readmission to hospital for heart failure or myocardial infarction in patients after an acute myocardial infarction, suggesting that this technique may serve as a valuable adjunctive procedure after myocardial infarction to prevent the development of heart failure and reduce the risk of future adverse events.

TRIAL REGISTRATION

ClinicalTrials.gov NCT05043610.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Stem cell therapy has beneficial effects on the function of the left ventricle (left ventricular ejection fraction) after acute myocardial infarction

WHAT THIS STUDY ADDS

Intracoronary infusion of Wharton's jelly derived mesenchymal stem cells within 3-7 days after acute myocardial infarction reduced the incidence of heart failure and its related hospital admission

Introduction

Advances in management of acute myocardial infarction have significantly improved survival rates, but this has also led to a rising incidence of post-myocardial infarction heart failure, now recognised as a major cause of morbidity worldwide.[1-3] Although the management of heart failure is well advanced, preventive measures for heart failure in patients after a myocardial infarction remain underexplored. Stem cell therapy has emerged as a promising intervention because it can support repair of cardiac tissue and preserve ventricular function.

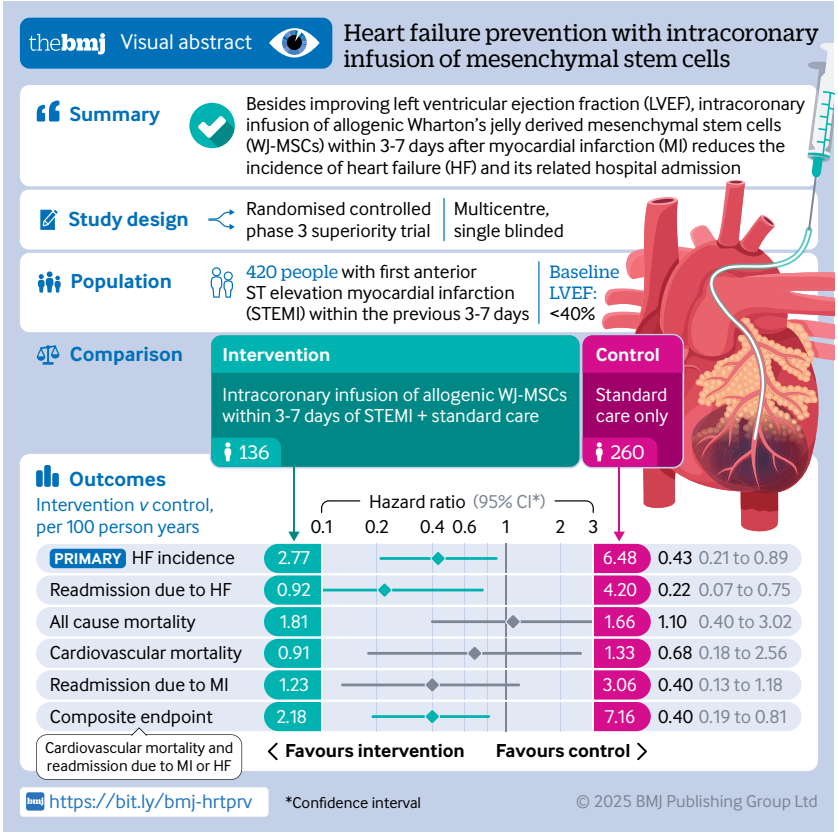
Despite growing interest, most clinical trials investigating stem cell therapy have been limited by small sample sizes and a focus on surrogate endpoints such as cardiac biomarkers, left ventricular ejection fraction, or scar size. Furthermore, most previous studies have had relatively short follow-up durations, often limited to less than a year, focusing mainly on early changes in left ventricular ejection fraction and short term outcomes. The BAMI trial, the largest phase 3 trial in this area, used total mortality as its primary endpoint but did not show a significant benefit, despite

a significant reduction in hospital admissions for heart failure after intracoronary infusion of bone marrow derived mononuclear cells.[4] These findings highlight the challenges of using mortality as a primary endpoint in cell therapy trials and suggest that incidence of heart failure may be a more appropriate and sensitive clinical outcome for evaluating efficacy.

Mesenchymal stem cells have shown greater promise than bone marrow derived mononuclear cells for treating patients with acute myocardial infarction.[5-7] Moreover, the overall safety profile of mesenchymal stem cells, combined with the ease of isolating Wharton's jelly derived mesenchymal stem cells and their ex-vivo expansion, in-vitro proliferation, and immune privileged properties, further supports their potential as a viable therapeutic option for cardiac regeneration.[8] Our previous phase 2 trial showed the effectiveness of intracoronary infusion of Wharton's jelly derived mesenchymal stem cells in improving left ventricular ejection fraction after myocardial infarction.[9] Building on these insights, we designed a phase 3 clinical trial with long term follow-up to assess the effect of intracoronary infusion of Wharton's jelly derived mesenchymal stem cells on the development of post-myocardial infarction heart failure.

Methods

The comprehensive protocol is explained in the supplementary materials. This manuscript has been prepared in adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.



Study design

The PREVENT-TAHA8 trial is a single blinded, randomised, phase 3 superiority trial conducted from September 2021 to October 2024. It evaluated the effect of intracoronary infusion of Wharton's jelly derived mesenchymal stem cells from umbilical cord as an adjunct to standard therapy on reducing the incidence of heart failure following acute myocardial infarction compared with standard treatment alone. The Traditional and Advanced Heart Approaches (TAHA) clinical trials group designed, conducted, and coordinated this study.

Study population

We enrolled patients aged 18 to 65 years who had experienced their first acute anterior ST segment elevation myocardial infarction within the previous three to seven days, had a left ventricular ejection fraction <40% as indicated by echocardiography, and were successfully treated with primary percutaneous coronary intervention. Patients with a history of previous cardiac conditions (valvular, ischaemic, or congenital disorders), poor echocardiography window, regional wall motion abnormalities outside the region of the infarction, left ventricle dysfunction due to other causes (such as non-ischaemic cardiomyopathy, anthracycline use, or ethanol misuse), active infection, malignancy, or autoimmune disease were excluded from the study. A negative pregnancy test was required for female patients of reproductive age before they were included in the study.

Consent

All patients gave informed consent. A trained physician provided each participant with a detailed explanation of the study's purpose, the investigational nature of the therapy, the potential benefits, and all known or anticipated risks. Patients were advised to adhere to all scheduled follow-up visits promptly, report any adverse events or hospital admissions, and consult with the study team before starting any new medical or surgical treatments. The consent process was conducted in accordance with the Declaration of Helsinki, upholding the principles of autonomy and respect for persons. It was approved by the appropriate institutional review board and ethics committee. Before consent acquisition, all relevant information was discussed thoroughly with potential participants.

Sample size, randomisation, and blinding

Given that the intervention involves intracoronary infusion of Wharton's jelly derived mesenchymal stem cells, which remains an experimental therapy, and aiming to minimise the number of participants exposed to the novel intervention while maximising comparative efficacy and statistical power in between group analysis, we chose a 1:2 randomisation ratio (intervention to control). We initially calculated the sample size to include approximately 118 patients in the intervention arm and 220 patients in the control arm to detect a difference in heart failure incidence

rate, assuming rates of 3.9% in the intervention group and 12% in the control group on the basis of the results from the BAMI trial. To ensure adequate statistical power to enable adjustment for at least three to five covariates, we needed a minimum of 30-40 heart failure events in the total population. To accommodate this and enhance the robustness and reliability of the treatment effect estimation, we increased the sample size to 390 participants. Additionally, considering the novelty of the intervention and the logistical challenge of a three to seven day gap between primary percutaneous coronary intervention and intracoronary infusion of mesenchymal stem cells, we anticipated a rate of dropout and consent withdrawal of 8-10%. The final recruitment target was set at 420 participants to compensate for these potential dropouts. Randomisation was done centrally at the main study centre by using permuted block randomisation (block size of six), implemented through a web based randomisation system (https://www.sealedenvelope.com/randomisation/simulation/). The random sequence was generated and maintained through this platform by the interventional cardiologist, who was solely responsible for administering the mesenchymal stem cell infusion and for scheduling the procedure accordingly. This cardiologist, along with the staff involved in the infusion procedure, had no role in following up patients, assessing outcomes, or analysing data. Ethics committee and institutional review board restrictions meant that a sham procedure was not permitted and patients could not be blinded to allocation. However, all researchers, clinicians, and staff members responsible for follow-up care, outcome adjudication, and data analysis remained blinded. Participants were clearly instructed not to reveal their group allocation to clinical staff unless a serious adverse event occurred. Thus, we conducted the trial as a single blind study. Additional details on sample size calculation, randomisation, and blinding are available in the supplementary materials.

Intracoronary infusion of mesenchymal stem cells

Patients in the intervention group underwent intracoronary infusion of an estimated 10^7 Wharton's jelly derived mesenchymal stem cells in the cardiac catheterisation laboratory. Clinical grade, current good manufacturing practice certified allogenic human Wharton's jelly derived mesenchymal stem cells were transported to the hospital on the day of the infusion and suspended in 0.9% saline. Patients with an activated clotting time <200 s received a weight based heparin bolus. A therapeutic 6 Fr guiding catheter was inserted into the left coronary artery, and 200 µg of nitroglycerin was infused. The TIMI (Thrombolysis in Myocardial Infarction) flow in the left anterior descending artery was assessed and documented. A 0.014 inch, soft tipped guide wire was inserted into the left anterior descending artery at the distal edge of the stent. An over-the-wire balloon was guided to the stented area and inflated to achieve occlusion. After removal of the guide wire, the mesenchymal stem cells were infused at a rate of 2.5 mL/min, with a total infusion volume of 7.5 mL, divided into three portions. After each portion, TIMI coronary flow was reassessed with contrast dye. Once the cells were delivered, a coronary flow wire was placed via the micro-infusion catheter.

The mesenchymal stem cells used in our study were sourced from Wharton's jelly derived mesenchymal stem cells. The umbilical cords used for isolation of Wharton's jelly derived mesenchymal stem cells came from full term births of baby boys. Data on maternal health status were collected, and the eligibility criteria for healthy donors for the Wharton's jelly derived mesenchymal stem cells biobank were met. Cells were isolated using a standard enzymatic digestion followed by centrifugation, ensuring a uniform cell population. We adhered to the minimal criteria established by the International Society for Cell and Gene Therapy (ISCT) to characterise mesenchymal stem cells.[10] Initially, the plastic adherence of the mesenchymal stem cells was verified under standard culture conditions. Then, flow cytometry analysis showed the expression of surface markers CD105, CD73, and CD90, whereas the cells were negative for CD45, CD34, CD11b, CD31, and HLA-DR, aligning with ISCT standards.[10 11] Furthermore, the mesenchymal stem cells showed the ability to differentiate into adipocytes, osteoblasts, and chondrocytes under defined in vitro conditions.[12 13] The cells were expanded in a xeno-free culture medium, with adherence to good manufacturing practice guidelines to ensure consistency and safety for clinical use.[10] Each batch of mesenchymal stem cells was subjected to stringent quality control protocols, including sterility testing, endotoxin analysis, surface markers, and viability assessments to ensure consistency across batches. The Wharton's jelly derived mesenchymal stem cells used in our study have previously been evaluated specifically for treating acute myocardial infarction.[9]

Study outcomes

The primary endpoint was the incidence of heart failure, defined as a clinical condition with symptoms of dyspnoea at rest or during exertion and evidence of cardiogenic pulmonary or systemic congestion necessitating an outpatient visit, hospital admission, or emergency department visit during which medical therapy was administered for symptoms and signs consistent with cardiac decompensation or impaired cardiac function. To complement this, we evaluated readmission to hospital for heart failure as a secondary outcome, providing an objective measure that may reduce diagnostic bias and allowing for integration into composite cardiovascular endpoints. Other secondary outcomes included all cause mortality, cardiovascular mortality, readmission to hospital for myocardial infarction, and relevant composite endpoints encompassing major adverse cardiovascular events. To assess the physiological effect of the intervention, we also evaluated changes in left ventricular ejection fraction during the

third scheduled follow-up visit, which occurred approximately six months after discharge (ranging from four to eight months). Detailed definitions of all endpoints are provided in the supplementary materials. Physicians (cardiologists) responsible for patient care and follow-up evaluated cardiovascular events and left ventricular ejection fraction. Then, outcome assessors investigated the patients' medical records and documents to confirm the outcome. These assessors were blinded to treatment allocation to ensure objectivity. Before statistical analysis, an experienced cardiologist not involved in the study design, data analysis, or patient care adjudicated all measurements. This adjudicator, who was also blinded to group allocation, evaluated the quality of each measurement and excluded any inadequate data, which we treated as missing in the final analysis. An independent, blinded safety committee (data safety and monitoring board committee) was responsible for evaluating potential major adverse cardiac events to ensure objective assessment of safety outcomes.

Patient care

During the hospital course, patients received standard protocol management. Signs and symptoms at admission were recorded, and routine monitoring, daily physical examinations, laboratory tests, and electrocardiography were conduced. Cardiac evaluations, including echocardiography, were completed before the intervention, with left ventricular ejection fraction determined by Simpson's rule. After the intervention and once haemodynamically stable, all patients, regardless of study arm, received standard evidence based treatment for acute myocardial infarction such as antiplatelet therapy (aspirin with either ticagrelor or clopidogrel), statins, and glyceryl trinitrate, as clinically indicated. All the patients received a β blocker and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker if not contraindicated. For patients with diabetes, a mineralocorticoid receptor antagonist was added and continued unless the left ventricular ejection fraction rose above 40% and no sign of heart failure was present. If a patient developed heart failure with reduced ejection fraction, specific measures included the replacement of a combination of sacubitril/valsartan (combination dosage started from 24/26 mg twice daily and up-titrated to 97/103 mg if the patient could tolerate it) instead of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, addition of aldosterone receptor antagonists (eplerenone or spironolactone started from 25 mg daily dosage and up-titrated to 100 mg if the patient could tolerate it), and prescription of sodium-glucose cotransporter 2 inhibitors (10 mg empagliflozin or dapagliflozin daily). On the basis of clinical symptoms, other measures such as addition of diuretics were also considered. All patients were also screened for eligibility for an implantable cardioverter-defibrillator or cardiac resynchronisation therapy according to guideline directed criteria. The first follow-up visit was scheduled for 10 days after discharge, followed by structured outpatient visits every three months, which included electrocardiography, cardiovascular assessments, and tailored patient centred care. All patients were closely monitored and participated in a cardiac rehabilitation programme. Follow-up and care continued for a total of three years.

Covariates

The covariates included age, sex, baseline left ventricular ejection fraction, smoking status, obesity (defined as body mass index ≥30), anaemia, hypertension, diabetes, hypercholesterolaemia, and renal insufficiency. We analysed age and baseline left ventricular ejection fraction as both continuous and categorical variables, using cut-off values of 60 years for age and 30% for left ventricular ejection fraction. We defined anaemia, hypertension, diabetes, and hypercholesterolaemia on the basis of medical history, laboratory results, and the use of relevant medications. We determined renal insufficiency by using an estimated glomerular filtration rate of <60 mL/min/1.73 m^2, calculated using the modification of diet in renal disease formula.

Analysis population and handling of missing data

All participants who completed at least one post-discharge follow-up visit were included in the final analysis. We excluded patients who withdrew consent before discharge from hospital or declined to participate in any follow-up visits, owing to the complete absence of outcome data. For all included participants, we analysed clinical events and follow-up data up to their last available follow-up date. In time-to-event analyses, we treated this last follow-up point as the censoring time for patients who did not have the event of interest.

Statistical analysis

We presented continuous variables as means and standard deviations and categorical data as frequencies and percentages. We compared the baseline characteristics of the two study groups by using an independent sample Student's t test and Mann-Whitney U test for continuous variables and χ^2 and Fisher's exact tests for categorical variables. We used the Kruskal-Wallis and Shapiro-Wilk normality tests to assess the normality of continuous variables. We used Kaplan-Meier curves and log-rank tests to analyse the time-to-event data, providing insights into the patterns of endpoints over time. We also evaluated and depicted Nelson-Aalen estimates of cumulative hazard ratios. We used Kaplan-Meier survival analysis to estimate the cumulative probability (failure rate) of events at a three year follow-up, representing the probability of the event occurring within 36 months. We calculated the annual incidence rate by dividing the total number of events by the total person time at risk, expressed per 100 person years. We calculated confidence intervals for the incidence rate by using the Poisson approximation, on the basis of the number

of events and person time at risk. Analyses followed an intention-to-treat approach, and we determined statistical significance by using two sided P values with a threshold of P<0.05.

We used Cox proportional hazards regression models to compare primary and secondary endpoints between study groups, adjusting for covariates. We present optimised models in the paper; adjusted models for covariates are available in the supplementary materials. We initially developed a saturated model to obtain the optimised model, including treatment allocation and all covariates. We then did backwards elimination, sequentially removing the covariate with the highest P value until all remaining variables had P values <0.05. We assessed the interaction between treatment allocation and gender through an interaction analysis. Furthermore, we evaluated the proportional hazards assumption by using the global test on the basis of scaled Schoenfeld residuals, with results reported in the supplementary materials. Moreover, we did subgroup analyses for all covariates to explore potential differences in the effect of the intervention across subgroups.

To analyse improvement in left ventricular ejection fraction within six months after acute myocardial infarction, we did a Wilcoxon matched pairs signed rank test to assess differences between post-six month left ventricular ejection fraction and baseline left ventricular ejection fraction within both the intervention and control groups. We used the Wilcoxon rank-sum test to compare changes in left ventricular ejection fraction between treatment groups. We considered a two sided P value <0.05 to be statistically significant for these Wilcoxon rank tests. Additionally, we did a linear regression analysis to examine the effect of group assignment on change in left ventricular ejection fraction. We used Stata version 18 for all statistical analysis.

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting, or dissemination planning of this study. Given the investigational nature of the intervention and the general lack of public awareness about stem cell therapies, particularly in the context of cardiovascular health, our efforts were primarily directed towards enhancing understanding and engagement through education and transparent communication. To reduce this knowledge gap, we developed accessible educational brochures and shared study information via social media platforms across participating centres. These strategies aimed to raise awareness and support informed participation by improving patients' comprehension of the research and its objectives. Looking ahead, to enhance patient cooperation and community engagement in future trials, communicating the outcomes of this study widely through scientific publications, healthcare

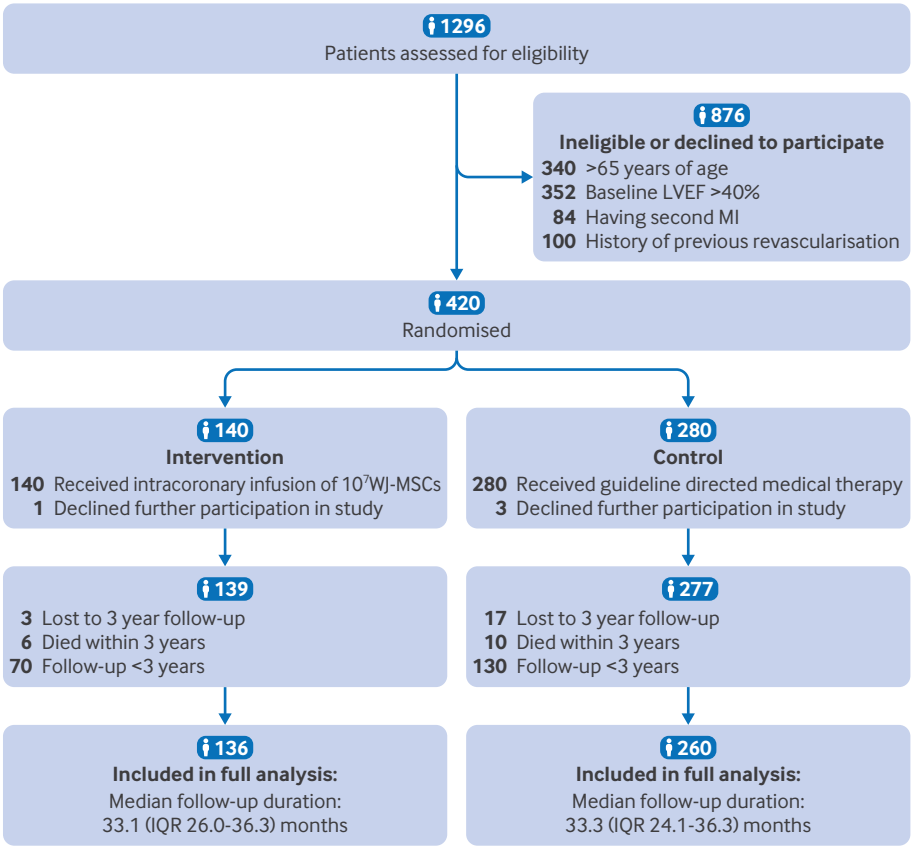


Fig 1 | CONSORT diagram of patient flow in PREVENT-TAHA8 trial. IQR=interquartile range; LVEF=left ventricular ejection fraction; MI= myocardial infarction; WJ-MSC=Wharton's jelly derived mesenchymal stem cells

institutions, academic forums, and public platforms, including social media will be essential. Increasing public understanding of regenerative medicine will be essential for broader participation and informed decision making in future studies.

Results

Patients and allocation

Figure 1 shows the CONSORT flow diagram of the study. Between September 2021 and November 2022, we recruited 420 patients with acute ST segment elevation myocardial infarction with the left anterior descending artery as the infarct related artery and left ventricular ejection fraction <40%, from which 140 patients were randomised to the intervention group (intracoronary infusion of Wharton's jelly derived mesenchymal stem cells in addition to standard treatment) and 280 patients to the control arm (standard treatment alone). One patient in the intervention group and three patients in the control group withdrew consent during the hospital admission and were excluded from further participation. Additionally, three patients in the intervention group and 17 in the control group did not attend the first scheduled follow-up visit and explicitly declined to continue in the study, despite attempts to contact them. After accounting for these drop-outs, we analysed data from 136 patients in the intervention group and 260 patients in the control group. The median follow-up period was 33.2 (interquartile range 24.6-36.3) months.

Baseline characteristics

Table 1 summarises and compares the baseline characteristics of the intervention and control arms. The mean age of participants was similar in the two groups: 57.8 (standard deviation 10.7) years for

Table 1 | Baseline characteristics of patients in PREVENT-TAHA8 trial. Values are numbers (percentages) unless stated otherwise

Characteristics	WJ-MSC (n=136)	Control (n=260)	Total (n=396)
Demographics			
Male sex	115 (85)	205 (79)	320 (81)
Mean (SD) age, years	57.8 (10.7)	59.2 (10.9)	58.7 (10.8)
Mean (SD) time to intracoronary infusion, days	5.8 (1.4)	-	-
Smoking	73/124 (59)	137/222 (62)	210/346 (61)
Mean (SD) BMI	27.6 (4.8)	27.6 (4.3)	27.6 (4.4)
BMI <25	33/117 (28)	63/208 (30)	96/325 (30)
BMI 25-30	56/117 (48)	94/208 (45)	150/325 (46)
BMI >30	28/117 (24)	51/208 (25)	79/325 (24)
Signs at admission			
Mean (SD) heart rate, bpm	77.7 (13.6) (n=123)	77.3 (12.3) (n=222)	77.4 (12.7) (n=345)
Mean (SD) systolic blood pressure, mm Hg	116.1 (15.7) (n=135)	115.4 (18.1)	115.6 (17.3) (n=395)
Mean (SD) diastolic blood pressure, mm Hg	71.1 (9.8) (n=135)	70.4 (12.1)	70.6 (11.3) (n=395)
Mean (SD) body temperature, °C	36.5 (0.5) (n=108)	36.6 (0.5) (n=203)	36.5 (0.5) (n=311)
Medical history			
Hypertension	57 (42)	117 (45)	174 (44)
Diabetes	25/124 (20)	30/222 (14)	55/346 (16)
Hypercholesterolaemia	42 (31)	85 (33)	127 (32)
Cerebrovascular accident	6/124 (5)	9/221 (4)	15/345 (4)
Peripheral vascular disease	0/124 (0)	3/221 (1)	3/345 (1)
Renal insufficiency	5/124 (4)	5/221 (2)	10/345 (3)
Laboratory findings			
Mean (SD) eGFR, mm/min/1.73 m^2	80.3 (20)	81.9 (19.9)	81.3 (19.9)
eGFR <90 mm/min/1.73 m^2	87 (64)	161 (62)	248 (63)
eGFR <60 mm/min/1.73 m^2	18 (134)	39 (1)	57 (14)
Anaemia	23 (17)	52 (20)	75 (19)
Echocardiographic findings			
Mean (SD) baseline LVEF, %	33.0 (4.9)	33.6 (5.0)	33.4 (5.0)
LVEF <30	33 (24)	61 (23)	94 (24)
Hospital administered drugs			
Aspirin	130 (96)	254/258 (98)	384/394 (97)
Clopidogrel	35 (26)	85/259 (33)	120/395 (30)
Ticagrelor	59 (43)	110/258 (43)	169/394 (43)
β blocker	122 (90)	234/258 (91)	356/394 (90)
Morphine	42/124 (34)	82/221 (37)	124/345 (36)
Statin	127 (93)	250/258 (97)	377/394 (96)
Angiotensin receptor blocker	18 (13)	20/258 (8)	38/394 (10)
Angiotensin converting enzyme inhibitor	116 (85)	215/258 (83)	331/394 (84)
Diuretic	52/124 (42)	92/221 (42)	144/345 (42)
Anti-arrhythmic agent	8/124 (6)	25/221 (11)	33/345 (10)
Aldosterone blocker	54 (40)	95/259 (37)	149/395 (38)
Unfractionated heparin	83/124 (67)	159/221 (72)	242/345 (70)
Low molecular weight heparin	60/124 (48)	118/221 (53)	178/345 (52)

BMI=body mass index; eGFR=estimated glomerular filtration rate; LVEF=left ventricular ejection fraction; SD=standard deviation; WJ-MSC=Wharton's jelly derived mesenchymal stem cells.

Table 2 | Number of events, failure rates, and annual incidence rates of endpoints in the Prevent-TAHA8 trial

Endpoints	Intervention (WJ-MSCs)			Control		
	No of total events/person years' follow-up	Cumulative probability* at 3 years' follow-up—% (95% CI)	Annual incidence rate—% (95% CI)†	No of total events/person years' follow-up	Cumulative probability* at 3 years' follow-up—% (95% CI)	Annual incidence rate—% (95% CI)†
HF incidence (development)	9/314.47	5.74 (1.99 to 9.50)	2.77 (1.44 to 5.32)	37/551.88	16.08 (10.90 to 21.27	6.48 (4.69 to 8.94)
Readmission to hospital for HF	3/325.39	2.48 (0.80 to 7.48)	0.92 (0.30 to 2.86)	24/570.98	10.77 (7.24 to 15.88	4.20 (2.82 to 6.27)
All cause mortality	6/331.24	5.85 (2.59 to 12.93)	1.81 (0.81 to 4.03)	10/602.66	4.43(2.39 to 8.13	1.66 (0.89 to 3.08)
Cardiovascular mortality	3/331.24	2.79 (0.89 to 8.61)	0.91 (0.29 to 2.81)	8/602.66	3.63 (1.81 to 7.18	1.33 (0.66 to 2.65)
Readmission to hospital for MI	4/325.34	3.88 (1.43 to 10.33)	1.23 (0.46 to 3.28)	18/588.63	8.38 (5.31 to 13.10	3.06 (1.93 to 4.85)
Composite of cardiovascular death and readmission for HF or MI	9/321.81	8.30 (4.32 to 15.61)	2.80 (1.45 to 5.37)	40/558.59	18.00 (13.40 to 23.94	7.16 (5.25 to 9.76)

CI=confidence interval; HF=heart failure; MI=myocardial infarction; WJ-MSC=Wharton's jelly derived mesenchymal stem cells.
*Estimated failure rates.
†Per 100 person years.

the intervention group and 59.2 (10.9) years for the control group. Most patients were male: 85% in the intervention group and 79% in the control group. All baseline characteristics and potential confounders, including left ventricular ejection fraction, previous medical conditions, signs at admission, and hospital administered drugs, were well balanced between the two groups.

Incidence of endpoints

We assessed the incidence of the endpoints at the three year follow-up and calculated the estimated failure rate and average annual incidence rate, as shown in table 2. In the intervention group, the failure rate of development of heart failure and readmission to hospital for heart failure at three years was 5.74% (95% confidence interval (CI) 1.99% to 9.50%) and 2.48% (0.80% to 7.48%), with an average annual incidence rate of 2.77% (1.44% to 5.32%) and 0.92% (0.30% to 2.86%), respectively. By contrast, the control group had a significantly higher event rate of heart failure development and readmission to hospital for heart failure at three years of 16.08% (95% CI 10.90% to 21.27%) and 10.77% (7.24% to 15.88%), with an average annual incidence rate of 6.48% (4.69% to 8.94%) and 4.20% (2.82% to 6.27%), respectively. We also observed this pattern in the composite endpoint of mortality and readmission to hospital for heart failure or myocardial infarction (supplementary table D).

Endpoint analysis

Kaplan-Meier survival estimates for the primary endpoint showed a statistically significant reduction in incidence of heart failure and readmission to hospital for heart failure in the intervention group compared with the control group (log-rank test, P=0.020 and 0.007, respectively). The cumulative hazard ratios for these endpoints remained consistently lower in the intervention group throughout the three years. For other secondary endpoints, the incidence of readmission to hospital for myocardial infarction was lower in the intervention group than in the control group, although this difference did not reach statistical significance (log-rank test, P=0.087). The groups had no significant differences in all cause and cardiovascular mortality (log-rank tests, P=0.856 and 0.567, respectively), with cumulative hazard ratios being similarly matched. Furthermore, the intervention group had lower incidences of the composite endpoint of cardiovascular mortality and readmission to hospital for heart failure or myocardial infarction than did the control group, with significantly lower cumulative hazards for this composite endpoint over the follow-up period (log-rank test, P=0.009). Figure 2 and table 2 show detailed results of the Nelson-Aalen estimates of cumulative hazard ratios, log-rank test results, failure rates, and cumulative hazard ratios at one, two, and three years of follow-up. These findings for other composite endpoints are detailed in supplementary figure A and supplementary tables B and C.

As shown in figure 3, unadjusted Cox regression analysis showed that intracoronary infusion of Wharton's jelly derived mesenchymal stem cells had a protective effect against development of heart failure (crude hazard ratio 0.43, 95% CI 0.21 to 0.89) and readmission to hospital for heart failure (0.22, 0.06 to 0.74). Additionally, it showed significant protective effects on the composite endpoint of cardiovascular mortality and readmission to hospital for heart failure or myocardial infarction (crude hazard ratio 0.40, 0.19 to 0.82). After adjustment for age, sex, and baseline left ventricular ejection fraction, the protective effect of intracoronary infusion of Wharton's jelly derived mesenchymal stem cells as an adjunct procedure against these endpoints remained significant (supplementary table E). Models further adjusted for smoking and obesity were not statistically valid owing to a high proportion of missing data and an insufficient event-to-covariate ratio. The Cox regression analyses of outcomes with different adjustment levels are shown in supplementary table E. In the final optimised model for both heart failure incidence and readmission to hospital for heart failure, treatment allocation and sex were the only covariates retained. Female patients were at a higher risk of developing heart failure (adjusted hazard ratio 2.19, 95% CI 1.18 to 4.06) and readmission to hospital for heart failure (2.50, 1.14 to 5.46) compared with male patients. Details of the

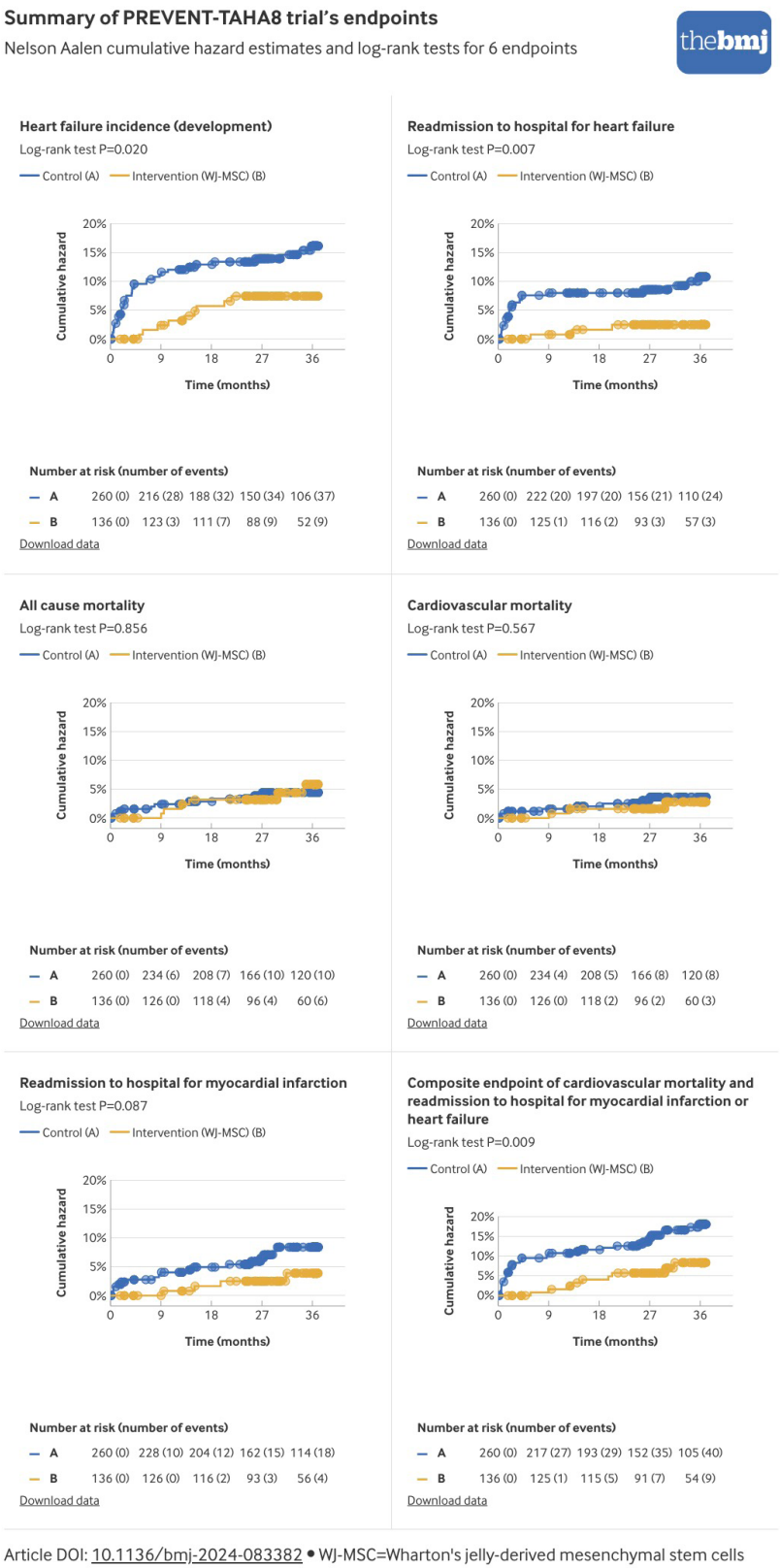


Fig 2 | Cumulative hazard estimates and log-rank test of PREVENT-TAHA8 trial's endpoints: heart failure (HF) incidence (development) (primary endpoint), readmission to hospital for HF, all cause mortality, cardiovascular mortality, readmission to hospital for myocardial infarction (MI), and composite endpoint of cardiovascular mortality and readmission to hospital for HF or MI. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/25452455/

optimised Cox regression models are summarised in the table in figure 3 and supplementary table F. Additionally, subgroup analyses showed no significant variation in the effect of the intervention across different patient subgroups (supplementary table H).

Changes in left ventricular ejection fraction at six month follow-up

Left ventricular ejection fraction improved significantly in both the intervention and control groups from baseline to six months. However, the improvement was significantly greater in the intervention group than in the control group (fig 4). Moreover, linear regression analysis confirmed that treatment allocation was a significant predictor of change in left ventricular ejection fraction, with the intervention group showing a mean increase of approximately six percentage points compared with the control group (β=5.88%, 95% CI 4.00% to 7.76%; P<0.001). These findings remained consistent in the linear regression analysis after adjustment for covariates (supplementary materials).

Adverse events and safety

During the hospital stay, the patients were closely monitored for any adverse events, including arrhythmia, hypersensitivity reaction, re-infarction, and many other conditions. The focus on long term follow-up was to monitor tumour formation. No adverse events were noticed.

Discussion

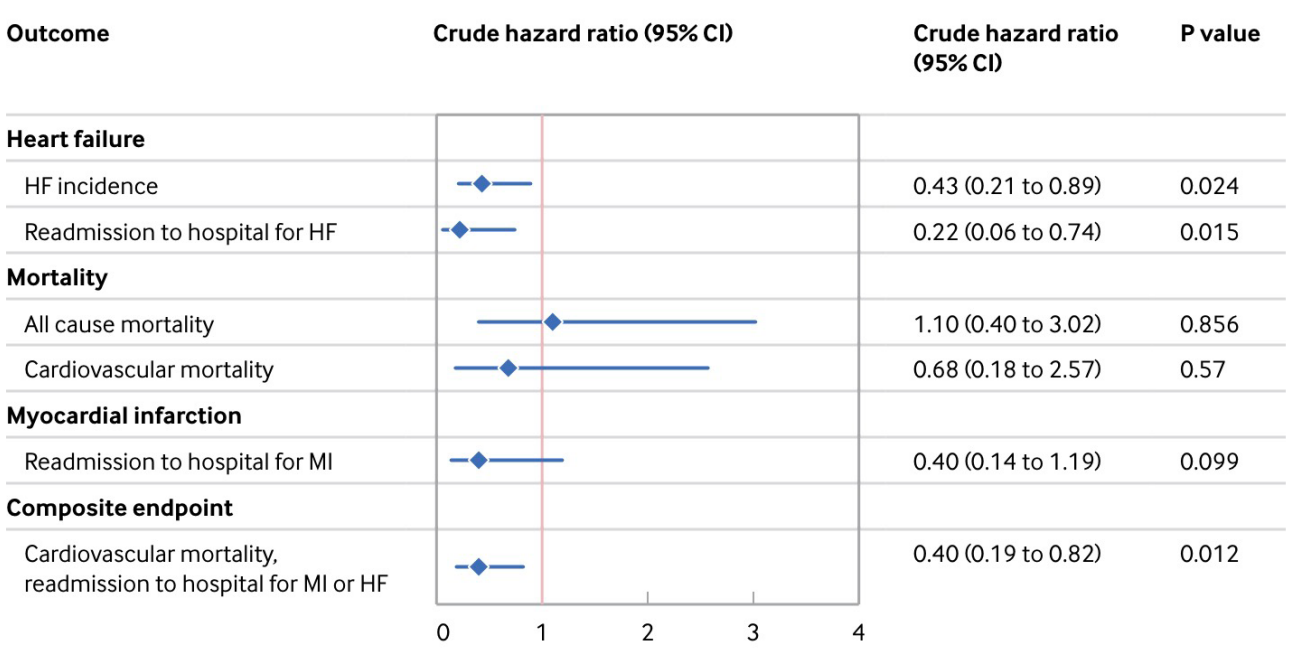
The PREVENT-TAHA8 study showed that intracoronary infusion of Wharton's jelly derived mesenchymal stem cells can effectively prevent heart failure incidence, readmission to hospital for heart failure, and composite endpoints of adverse events, including a composite endpoint of cardiovascular mortality and readmission to hospital for myocardial infarction or heart failure over three years, in patients having their first acute ST segment elevation myocardial infarction with impaired left ventricular ejection fraction. We also found that intracoronary infusion of mesenchymal stem cells, when added to standard care, led to a significantly greater improvement in left ventricular ejection fraction at six months post-myocardial infarction than standard treatment alone by approximately 6%. As a phase 3 trial evaluating the intracoronary infusion of mesenchymal stem cells in patients with ST segment elevation myocardial infarction, the findings position this intervention as a viable adjunctive procedure to mitigate myocardial infarction induced heart failure. Distinguishing this trial from other studies in this field are its focus on clinical endpoints rather than surrogate markers such as left ventricular ejection fraction and the use of Wharton's jelly derived mesenchymal stem cells instead of bone marrow derived mononuclear cells.

Comparison with other studies

The BAMI trial, which was the largest study designed to assess the efficacy of intracoronary infusion of bone marrow derived mononuclear cells in reducing

Cox regression analysis for endpoints in PREVENT-TAHA8 trial

Crude hazard ratios



Download data

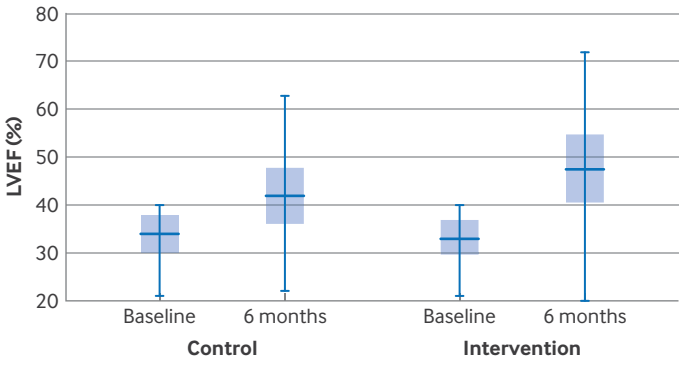
Outcome	Covariates	Hazard ratio (95% CI)	P value
HF incidence	Intervention v control	0.44 (0.21 to 0.91)	0.028
	Female v male	2.19 (1.18 to 4.06)	0.013
Readmission to hospital for HF	Intervention v control	0.23 (0.07 to 0.78)	0.018
	Female v male	2.50 (1.14 to 5.46)	0.022

Article DOI: 10.1136/bmj-2024-083382

HF=heart failure; MI=myocardial infarction; CI=confidence interval

Fig 3 | Crude and optimized Cox regression analysis for endpoints in PREVENT-TAHA8 trial. Top: crude hazard ratios from Cox regression analysis for trial endpoints. Bottom: optimised Cox regression models analysing treatment allocation and covariates for incidence of heart failure (HF) and readmission to hospital for HF. An interactive version of this graphic and downloadable data are available at https://public.flourish.studio/visualisation/25427034/

mortality following acute myocardial infarction, served as inspiration for our research. In BAMI, the rate of readmission to hospital for heart failure over two years was 2.7% (95% CI 1.0% to 5.9%; n=5) in the bone marrow derived mononuclear cells group compared with 8.1% (4.7% to 2.5%; n=15) in the control group.[4] In our study, the control group had a higher incidence rate and the intervention group had



	Baseline LVEF (%)	LVEF after 6 months	LVEF change	P value
Control	33.58 (5.04)	41.66 (8.95)	8.16 (7.81)	0.000
Intervention	32.97 (4.86)	47.14 (9.56)	14.28 (8.63)	0.000
P value of Wilcoxon rank sum test for comparison of LVEF change between groups				0.000

Fig 4 | Change in left ventricular ejection fraction (LVEF) at 6 month follow-up analysis. Top: box plot of baseline and 6 month LVEF. Bottom: Wilcoxon test results. Wilcoxon matched pairs signed rank test was used to assess differences between post-6 month LVEF and baseline LVEF within both intervention and control groups. To compare LVEF changes between treatment groups, Wilcoxon rank sum test was used

a lower rate compared with the BAMI results. Although the BAMI trial was halted before it reached the ultimate sample size, it indicated that readmission to hospital for heart failure, the primary endpoint of our study, could be prevented through intracoronary infusion of bone marrow derived mononuclear cells (hazard ratio 0.332, 95% CI 0.12 to 0.88) administered three to seven days after percutaneous coronary intervention.[4] Our findings corroborate this preventive potential and emphasise that this measure remains effective even after adjustment for confounding factors such as baseline left ventricular ejection fraction, age, and sex.

In the REPAIR-AMI trial, intracoronary infusion of bone marrow derived mononuclear cells was found to be preventive for readmission to hospital for heart failure at the one and two year follow-ups and for the combined endpoint of readmission for heart failure and mortality at the five year follow-up, although the results were not statistically significant.[14 15] Despite this insignificant effect, patients receiving intracoronary infusion of bone marrow derived mononuclear cells were shown to have greater improvement in left ventricular ejection fraction compared with the control group (5.5% (standard deviation 7.3%) versus 3.0% (6.5%)) at four months' follow-up.[16] This improvement was even higher in patients with left ventricular ejection fraction <40%, supporting our finding that Wharton's jelly derived mesenchymal stem cells therapy resulted in an approximate 6 unit increase in left ventricular ejection fraction change at six months compared with standard treatment alone. As our study exclusively involved patients with ST segment elevation myocardial infarction with baseline left ventricular ejection fraction <40%, the insignificant effects in earlier studies may be a result of the inclusion of patients with preserved left ventricular ejection fraction.

A meta-analysis of 23 clinical trials by Attar and colleagues, encompassing a total of 2286 patients, showed that the intracoronary infusion of bone marrow derived mononuclear cells is associated with a lower risk of the composite endpoint of hospital admission for heart failure, myocardial infarction, and cardiovascular mortality (91/1191 *v* 111/812; relative risk 0.643, 95% CI 0.489 to 0.845; P=0.002).[17] Most of these studies had small sample sizes and focused on endpoints such as left ventricular ejection fraction and cardiac markers [18-24], making the pooled analysis of endpoints a suitable method to assess the efficacy of intracoronary infusion of stem cells. By contrast, the PREVENT-TAHA8 trial, with a large sample size, showed that the composite endpoint of cardiovascular mortality and readmission to hospital for myocardial infarction or heart failure is significantly reduced by Wharton's jelly derived mesenchymal stem cell treatment (hazard ratio 0.40, 95% CI 0.19 to 0.82), consistent with the results from the REPAIR-AMI trial. This promising result highlights the potential of intracoronary infusion of mesenchymal stem cells as an adjunct procedure in primary percutaneous coronary intervention to prevent future adverse events in patients with acute myocardial infarction.

The reduced risk of a composite endpoint in previous studies was primarily the result of a decrease in rates of readmission to hospital for heart failure and myocardial infarction, rather than a reduction in mortality rates.[17] Similarly, the PREVENT-TAHA8 study found no significant differences in all cause and cardiac mortality between the intervention and control groups, mirroring results from the BAMI and REPAIR-AMI trials.[4 14 15] These findings suggest that mortality may be influenced by factors beyond the reach of stem cell therapy, including the type, timing, and management of myocardial infarction. However, as heart failure is the strongest predictor of death in patients with acute myocardial infarction, preventing heart failure may ultimately reduce mortality over longer follow-up periods, or very large sample sizes may be needed for detecting the effect of mesenchymal stem cells on mortality following myocardial infarction.[25]

In the final optimised models for heart failure incidence and readmission to hospital for heart failure, sex emerged as a significant predictor alongside treatment allocation. Female participants were at a higher risk than male participants for both outcomes, consistent with previous studies showing that women with myocardial infarction, particularly those with reduced ejection fraction, are more susceptible to developing heart failure and being readmitted to hospital.[26-28] However, the hazard ratios observed in our study were notably higher, approximately twofold to 2.5-fold, than those reported in the literature. This elevated risk may reflect known sex based disparities such as women tending to present with myocardial infarction at an older age, often with more atypical symptoms and a higher rate of complications,

contributing to poorer clinical outcomes. Importantly, our relatively young cohort (all participants <65 years) included a small number of female participants, which limits the precision of effect estimates and may have contributed to the higher hazard ratios observed. An exploratory interaction analysis between sex and treatment allocation (supplementary table G) showed that female participants in the control group had a significantly higher risk of heart failure than did male controls (hazard ratio 2.68, 95% CI 1.38 to 5.21). Notably, treatment with mesenchymal stem cells seemed to reduce this risk more substantially in female patients than in male patients, relative to male controls (hazard ratio 0.38 (95% CI 0.05 to 2.83) in female patients versus 0.60 (0.27 to 1.35) in male patients). Although these exploratory findings suggest a potential sex specific benefit of mesenchymal stem cell therapy, they should be interpreted with caution owing to the small sample size of female patients (unbalanced cohort) and the post hoc nature of the analysis. This observation warrants further investigation in future trials specifically designed to assess sex based differences in treatment response.

Readmission to hospital for myocardial infarction, as another adverse event after myocardial infarction, was reduced with injection of mesenchymal stem cells, although this reduction was not statistically significant. Cox analysis results in the BAMI and REPAIR-AMI trials similarly showed no significant reduction in myocardial infarction related readmission to hospital. In the REPAIR-AMI trial, the composite endpoint of readmission to hospital for myocardial infarction and mortality was significantly lower in the bone marrow derived mononuclear cells group at the one and two year follow-ups. In the DREAM-HF trial, subendocardial transplantation of mesenchymal stem cells in patients with congestive heart failure and an elevated high sensitivity C reactive protein concentration reduced the occurrence of re-infarction, which corroborates our findings.[29] These findings indicate that mesenchymal stem cells may have a preventive effect on the recurrence of myocardial infarction; more investigations with a larger sample size are needed to confirm this effect. This preventive effect of stem cell therapy may be attributed to the anti-inflammatory properties of mesenchymal stem cells, as evidenced by Perin and colleagues, who showed that the benefits of stem cell therapy are more pronounced in patients with baseline inflammation, indicated by higher concentrations of C reactive protein, in reducing the risk of non-fatal myocardial infarction or stroke in patients with heart failure.[29]

Mesenchymal stem cells can be derived from various sources, each with distinct biological properties that may influence the efficacy of therapy in cardiac regeneration.[12 30] In addition to mesenchymal stem cells, alternative cell types such as cardiosphere derived cells have been investigated for their potent immunomodulatory effects and their capacity to support myocardial regeneration.[31] Various delivery methods, including intracoronary infusion, intravenous injection, and transendocardial injection, have their own advantages and limitations. For instance, intracoronary infusion offers targeted delivery to the heart but may be limited by potential microvascular obstruction.[32] To optimise delivery techniques, recent studies have explored combining different delivery methods to improve cell retention and distribution.[33] Our previous phase 2 trial showed that a booster intracoronary dose of Wharton's jelly derived mesenchymal stem cells administered 10 days after the initial infusion resulted in greater improvement in left ventricular ejection fraction than a single dose injection.[9] Additionally, a separate phase 1 pilot study reported that combined intracoronary and intravenous transplantation of umbilical cord derived mesenchymal stem cells in patients ST segment elevation myocardial infarction with reduced left ventricular ejection fraction was safe and potentially effective in enhancing cardiac function.[34] These findings underscore the need to conduct further phase 1 and 2 studies aimed at identifying the most effective stem cell type, isolation technique, and delivery strategy to maximise the therapeutic potential of mesenchymal stem cells in cardiac regeneration.

Significant barriers remain in translating stem cell therapy into routine bedside management for cardiovascular patients. A major challenge is that many trials prioritise surrogate endpoints, such as left ventricular ejection fraction, as their primary focus. Although these markers can act as predictors of cardiovascular events, their fluctuations during different phases of recovery after myocardial infarction may complicate the interpretations. Therefore, directly assessing clinical endpoints as the primary study objectives is crucial to provide clear evidence of the benefits of bone marrow derived mononuclear cell or mesenchymal stem cell therapy.[35] Follow-up durations, as another key factor, in previous studies have varied considerably, with most limited to less than one year and primarily focused on changes in left ventricular ejection fraction. Longer term studies assessing clinical endpoints have produced inconsistent results, possibly owing to the absence of robust mid-term follow-up data. The PREVENT-TAHA8 trial aimed to close this gap by providing mid-term (three years) outcome evidence to help to guide the design of future larger trials. Selecting an appropriate primary outcome is another critical consideration for future trials. On the basis of both existing literature and the findings of our study, recurrence of myocardial infarction and heart failure seem to be the most relevant clinical endpoints influenced by stem cell therapy, in contrast to mortality. Mortality remains a complex outcome to affect, and why stem cell therapy has not consistently shown benefit in this domain is not yet clear. This may be attributed to the requirement for very large sample sizes to detect a mortality effect, or it may reflect the underlying mechanisms of action

of stem cells, which may primarily affect functional and reparative pathways rather than directly altering survival. Additional challenges include identifying the optimal cell types, refining cell isolation and delivery methods, and tackling logistical and safety concerns, which require further phase 1 or 2 trials and adherence to the newest updates on definitions and protocols regarding stem cell therapy.[13]

Strengths and limitations of study

This study, by using mesenchymal stem cells instead of bone marrow derived mononuclear cells, enrolling a selected at risk population of patients, having a long term follow-up, enrolling the largest sample size in the field, and using a clinical endpoint instead of surrogate endpoints such as left ventricular ejection fraction, may have paved a new way in the field of regenerative cardiology.

The limitations of this study include the inability to do a sham procedure for the control group, which would have allowed for a double blinded study design instead of a single blinded format. We did not assess heart failure biomarkers or investigate the physiological effects of the intervention on cardiac tissue, such as through cardiac biopsy or advanced imaging, as these were beyond the scope of our study. However, such mechanistic evaluations will be essential in future trials to confirm the pathophysiological benefits of this adjunctive therapy and support its integration into routine clinical practice. Although we did not assess these effects, previous studies suggest that the therapeutic actions of mesenchymal stem cells are primarily mediated through paracrine signalling, promoting angiogenesis, modulating inflammation, and reducing fibrosis rather than through direct engraftment or structural repair of the myocardium.[36] The relatively small number of events and limited sample size restricted our ability to do statistically valid multivariable adjustments beyond key covariates such as sex, age, and baseline left ventricular ejection fraction. As a result, potential confounders such as obesity, smoking status, stress level, physical activity, education level, and socioeconomic status were not included in the final models. Future trials should incorporate these variables in both study design and data collection to enable more comprehensive adjustment and better understanding of their impact on treatment outcomes. Additionally, we were unable to enrol sufficient patients to enrich significant results for endpoints such as re-infarction. Another potential critique of our study may question the choice of intracoronary infusion over the transendocardial route for stem cell delivery. Although we acknowledge this as a limitation, the decision resulted from the unavailability of transendocardial catheters in our region and the lack of significant differences in improvement in left ventricular ejection fraction between the two methods, as shown by previous meta-analyses.[6]

Conclusion

The PREVENT-TAHA8 study provides compelling evidence that intracoronary infusion of Wharton's jelly derived mesenchymal stem cells significantly reduces the risk of heart failure incidence, readmission to hospital for heart failure, and the composite endpoint of mortality and readmission for heart failure or myocardial infarction in patients with ST segment elevation myocardial infarction with impaired left ventricular ejection fraction. Although the intervention did not significantly affect the recurrence of myocardial infarction or mortality, it highlights the potential of Wharton's jelly derived mesenchymal stem cells as a valuable adjunctive treatment in primary percutaneous coronary intervention to prevent future adverse events. Further research is needed to explore the underlying mechanisms of mesenchymal stem cells therapy and to optimise its application in clinical practice.

AUTHOR AFFILIATIONS

[1]Department of Cardiovascular Medicine, TAHA Clinical Trial Group, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Barts Heart Centre, Barts Health NHS Trust, London, UK

[3]Centre for Cardiovascular Medicine and Devices, William Harvey Research Institute, Queen Mary University of London, London, UK

[4]NIHR Barts Biomedical Research Centre, Queen Mary University of London, Charterhouse Square, London, UK

[5]Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[6]Department of Pathology, Shiraz University of Medical Sciences, Shiraz, Iran

[7]Department of Cardiology, School of Medicine, Sharjah University, Sharjah, UAE

[8]Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran

[9]Transplant Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

We are grateful to Hossein Molavi Vardanjani for his valuable assistance with statistical analysis and analytical guidance.

Contributors: AA, AMathur, and SD were involved in conceptualisation, methodology, patient management, procedures, administration, and supervision. SAM was involved in statistical analysis, visualisation, original draft writing, and final revision. FA, AMonabati, MV, NA, MK, and YK provided the stem cells and managed the safety, qualitative control of mesenchymal stem cells, data acquisition, and patient management. All authors helped in writing and editing the draft. They all read and critically revised the manuscript and approved the final format. AA is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: The study received funding from the Office of the Vice-Chancellor for Research of Shiraz University of Medical Sciences (grant numbers SG-98-5, SG-98-94, and SG-96-86). The funder had no role in the study, except that Shiraz University of Medical Sciences provided ethical clearance and most of the researchers are affiliated with Shiraz University of Medical Sciences. The National Institute for Medical Research Development also provided grant number 4001962. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, the writing of the report, or the decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Office of the Vice-Chancellor for Research of Shiraz University of Medical Sciences and the National Institute for Medical Research Development; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The trial adhered to the principles outlined in the Declaration of Helsinki. The study protocol received approval from the local institutional review board and ethics committee (approval code: IR.SUMS.REC.1400.409) and is registered on ClinicalTrials.gov with the identifier NCT05043610. Informed consent was obtained from all patients. The consent process was conducted in accordance with the Declaration of Helsinki, upholding the principles of autonomy and respect for persons. It was approved by the appropriate institutional review board and ethics committee.

Data sharing: De-identified individual participant data underlying the results reported in this article are available through the Figshare sharing platform (https://doi.org/10.6084/m9.figshare.29375153.v2).

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Participating sites were informed of the results. The results will be communicated to study participants who express an interest during clinic visits. Dissemination to the public will be achieved through media outreach.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Bahit MC, Kochar A, Granger CB. Post-myocardial infarction heart failure. *JACC Heart Fail* 2018;6:179-86. doi:10.1016/j.jchf.2017.09.015
2 Jenča D, Melenovský V, Stehlik J, et al. Heart failure after myocardial infarction: incidence and predictors. *ESC Heart Fail* 2021;8:222-37. doi:10.1002/ehf2.13144
3 Velagaleti RS, Pencina MJ, Murabito JM, et al. Long-term trends in the incidence of heart failure after myocardial infarction. *Circulation* 2008;118:2057-62. doi:10.1161/CIRCULATIONAHA.108.784215
4 Mathur A, Fernández-Avilés F, Bartunek J, et al, BAMI Group. The effect of intracoronary infusion of bone marrow-derived mononuclear cells on all-cause mortality in acute myocardial infarction: the BAMI trial. *Eur Heart J* 2020;41:3702-10. doi:10.1093/eurheartj/ehaa651
5 Gao LR, Chen Y, Zhang NK, et al. Intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells in acute myocardial infarction: double-blind, randomized controlled trial. *BMC Med* 2015;13:162. doi:10.1186/s12916-015-0399-z
6 Attar A, Bahmanzadegan Jahromi F, Kavousi S, Monabati A, Kazemi A. Mesenchymal stem cell transplantation after acute myocardial infarction: a meta-analysis of clinical trials. *Stem Cell Res Ther* 2021;12:600. doi:10.1186/s13287-021-02667-1
7 Heldman AW, DiFede DL, Fishman JE, et al. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: the TAC-HFT randomized trial. *JAMA* 2014;311:62-73. doi:10.1001/jama.2013.282909
8 Wang Y, Yi H, Song Y. The safety of MSC therapy over the past 15 years: a meta-analysis. *Stem Cell Res Ther* 2021;12:545. doi:10.1186/s13287-021-02609-x
9 Attar A, Farjoud Kouhanjani M, Hessami K, et al. Effect of once versus twice intracoronary injection of allogeneic-derived mesenchymal stromal cells after acute myocardial infarction: BOOSTER-TAHA7 randomized clinical trial. *Stem Cell Res Ther* 2023;14:264. doi:10.1186/s13287-023-03495-1
10 Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006;8:315-7. doi:10.1080/14653240600855905
11 Amanat M, Majmaa A, Zarrabi M, et al. Clinical and imaging outcomes after intrathecal injection of umbilical cord tissue mesenchymal stem cells in cerebral palsy: a randomized double-blind sham-controlled clinical trial. *Stem Cell Res Ther* 2021;12:439. doi:10.1186/s13287-021-02513-4
12 Stroncek DF, Jin P, McKenna DH, et al. Human Mesenchymal Stromal Cell (MSC) Characteristics Vary Among Laboratories When Manufactured From the Same Source Material: A Report by the Cellular Therapy Team of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative. *Front Cell Dev Biol* 2020;8:458. doi:10.3389/fcell.2020.00458
13 Renesme L, Cobey KD, Lalu MM, et al. Delphi-driven consensus definition for mesenchymal stromal cells and clinical reporting guidelines for mesenchymal stromal cell-based therapeutics. *Cytotherapy* 2025;27:146-68. doi:10.1016/j.jcyt.2024.10.008
14 Assmus B, Leistner DM, Schächinger V, et al, REPAIR-AMI Study Group. Long-term clinical outcome after intracoronary application of bone marrow-derived mononuclear cells for acute myocardial infarction: migratory capacity of administered cells determines event-free survival. *Eur Heart J* 2014;35:1275-83. doi:10.1093/eurheartj/ehu062
15 Schächinger V, Erbs S, Elsässer A, et al, REPAIR-AMI Investigators. Improved clinical outcome after intracoronary administration of bone-marrow-derived progenitor cells in acute myocardial infarction: final 1-year results of the REPAIR-AMI trial. *Eur Heart J* 2006;27:2775-83. doi:10.1093/eurheartj/ehl388
16 Schächinger V, Erbs S, Elsässer A, et al, REPAIR-AMI Investigators. Intracoronary bone marrow-derived progenitor cells in acute myocardial infarction. *N Engl J Med* 2006;355:1210-21. doi:10.1056/NEJMoa060186
17 Attar A, Hosseinpour A, Hosseinpour H, Kazemi A. Major cardiovascular events after bone marrow mononuclear cell transplantation following acute myocardial infarction: an updated post-BAMI meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord* 2022;22:259. doi:10.1186/s12872-022-02701-x
18 Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 2004;364:141-8. doi:10.1016/S0140-6736(04)16626-9
19 Wollert KC, Meyer GP, Müller-Ehmsen J, et al. Intracoronary autologous bone marrow cell transfer after myocardial infarction: the BOOST-2 randomised placebo-controlled clinical trial. *Eur Heart J* 2017;38:2936-43. doi:10.1093/eurheartj/ehx188
20 Lunde K, Solheim S, Aakhus S, et al. Intracoronary injection of mononuclear bone marrow cells in acute myocardial infarction. *N Engl J Med* 2006;355:1199-209. doi:10.1056/NEJMoa055706
21 Delewi R, van der Laan AM, Robbers LF, et al, HEBE investigators. Long term outcome after mononuclear bone marrow or peripheral blood cells infusion after myocardial infarction. *Heart* 2015;101:363-8. doi:10.1136/heartjnl-2014-305892
22 Lamirault G, de Bock E, Sébille V, et al. Sustained quality of life improvement after intracoronary injection of autologous bone marrow cells in the setting of acute myocardial infarction: results from the BONAMI trial. *Qual Life Res* 2017;26:121-5. doi:10.1007/s11136-016-1366-7
23 Sürder D, Manka R, Moccetti T, et al. Effect of Bone Marrow-Derived Mononuclear Cell Treatment, Early or Late After Acute Myocardial Infarction: Twelve Months CMR and Long-Term Clinical Results. *Circ Res* 2016;119:481-90. doi:10.1161/CIRCRESAHA.116.308639
24 Tendera M, Wojakowski W, Ruzyłło W, et al, REGENT Investigators. Intracoronary infusion of bone marrow-derived selected CD34+CXCR4+ cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial. *Eur Heart J* 2009;30:1313-21. doi:10.1093/eurheartj/ehp073
25 Granger CB, Goldberg RJ, Dabbous O, et al, Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345-53. doi:10.1001/archinte.163.19.2345
26 Wang X, Jering KS, Cikes M, et al. Sex Differences in Clinical Characteristics and Outcomes After Myocardial Infarction With Low Ejection Fraction: Insights From PARADISE-MI. *J Am Heart Assoc* 2023;12:e028942. doi:10.1161/JAHA.122.028942
27 Cenko E, Manfrini O, Yoon J, et al. Sex Differences in Heart Failure Following Acute Coronary Syndromes. *JACC Adv* 2023;2:100294. doi:10.1016/j.jacadv.2023.100294
28 Shen L, Wang L, Huang H, et al. Sex difference in the development and progression of heart failure after firsttime ST-elevation myocardial infarction. *J Am Coll Cardiol* 2025;85(Suppl):1790doi:10.1016/S0735-1097(25)02274-0.
29 Perin EC, Borow KM, Henry TD, et al. Randomized Trial of Targeted Transendocardial Mesenchymal Precursor Cell Therapy in Patients With Heart Failure. *J Am Coll Cardiol* 2023;81:849-63. doi:10.1016/j.jacc.2022.11.061
30 Paul D, Samuel SM, Maulik N. Mesenchymal stem cell: present challenges and prospective cellular cardiomyoplasty approaches for myocardial regeneration. *Antioxid Redox Signal* 2009;11:1841-55. doi:10.1089/ars.2009.2455

31 Majka M, Sułkowski M, Badyra B, Musiałek P. Concise Review: Mesenchymal Stem Cells in Cardiovascular Regeneration: Emerging Research Directions and Clinical Applications. *Stem Cells Transl Med* 2017;6:1859-67. doi:10.1002/sctm.16-0484
32 Guo Y, Yu Y, Hu S, Chen Y, Shen Z. The therapeutic potential of mesenchymal stem cells for cardiovascular diseases. *Cell Death Dis* 2020;11:349. doi:10.1038/s41419-020-2542-9
33 Leong YY, Ng WH, Ellison-Hughes GM, Tan JJ. Cardiac Stem Cells for Myocardial Regeneration: They Are Not Alone. *Front Cardiovasc Med* 2017;4:47. doi:10.3389/fcvm.2017.00047
34 Hsiao LC, Lin YN, Shyu WC, et al. First-in-human pilot trial of combined intracoronary and intravenous mesenchymal stem cell therapy in acute myocardial infarction. *Front Cardiovasc Med* 2022;9:961920. doi:10.3389/fcvm.2022.961920
35 Traverse JH, Henry TD, Moye' LA. Is the measurement of left ventricular ejection fraction the proper end point for cell therapy trials? An analysis of the effect of bone marrow mononuclear stem cell administration on left ventricular ejection fraction after ST-segment elevation myocardial infarction when evaluated by cardiac magnetic resonance imaging. *Am Heart J* 2011;162:671-7. doi:10.1016/j.ahj.2011.06.019
36 Clavellina D, Balkan W, Hare JM. Stem cell therapy for acute myocardial infarction: Mesenchymal Stem Cells and induced Pluripotent Stem Cells. *Expert Opin Biol Ther* 2023;23:951-67. doi:10.1080/14712598.2023.2245329

Web appendix: Supplementary materials