A Report on "Prevention of Acute Myocardial Infarction Induced Heart Failure by Intracoronary Infusion of Mesenchymal Stem Cells: Phase 3 Randomised Clinical Trial (PREVENT-TAHA8)" by Attar et al. (2025)

Reviewer 2

February 05, 2026

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isitcredible.com

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I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.

Plato, *The Apology of Socrates*, 21d

To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.

Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Attar, A., Mirhosseini, S. A., Mathur, A., Dowlut, S., Monabati, A., Kasaei, M., Abtahi, F., Kiwan, Y., Vosough, M., & Azarpira, N. (2025). Prevention of Acute Myocardial Infarction Induced Heart Failure by Intracoronary Infusion of Mesenchymal Stem Cells: Phase 3 Randomised Clinical Trial (PREVENT-TAHA8). *BMJ*, Vol. 391, e083382.

URL: https://doi.org/10.1136/bmj-2024-083382

Abstract Summary: This phase 3 randomized clinical trial found that intracoronary infusion of Wharton's jelly derived mesenchymal stem cells significantly reduced the risk of heart failure incidence, readmission for heart failure, and a composite endpoint of cardiovascular mortality/readmission in patients following acute myocardial infarction.

Key Methodology: Phase 3 single-blinded randomized clinical trial (1:2 ratio) comparing WJ-MSCs infusion plus standard care versus standard care alone in 396 patients with first ST segment elevation MI and LVEF <40%, with a median follow-up of 33.2 months.

Research Question: What is the effect of intracoronary infusion of mesenchymal stem cells on the development of post-myocardial infarction heart failure?

Summary

Is It Credible?

The PREVENT-TAHA8 trial, conducted by Attar et al., presents the results of a phase 3 randomized clinical trial investigating the efficacy of intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) in preventing heart failure following acute myocardial infarction. The authors report a striking clinical benefit, claiming that the intervention "significantly reduced the risk of incidence of heart failure" with a hazard ratio of 0.43 and similarly reduced a composite endpoint of cardiovascular mortality and readmission (p. 1). Furthermore, the study reports a physiological benefit, noting that the left ventricular ejection fraction (LVEF) in the intervention group showed a "significantly greater improvement from baseline at six months" compared with the control group, with a mean difference of approximately 5.88 percentage points (p. 1). These are substantial claims that, if robust, would represent a major advancement in regenerative cardiology.

However, the credibility of the primary clinical conclusion—that the therapy prevents heart failure—is severely compromised by the statistical methodology employed. The headline hazard ratio of 0.43 is derived from an "optimised" Cox regression model (p. 9). The authors state that this model was achieved through "backwards elimination," a data-driven process that retains variables based on statistical significance rather than clinical relevance (p. 5). When the authors applied more rigorous, pre-planned models adjusting for standard confounders such as age, baseline ejection fraction, smoking, and obesity, the statistical significance of the treatment effect disappeared. As shown in the supplementary materials, "Model 3" yielded a non-significant hazard ratio of 0.58 (95% CI 0.27–1.23; $p = 0.158$), and "Model 4," which adjusted for comorbidities, was also non-significant (Supplementary p. 30). The authors justify relying on the simpler, significant model by claiming the ad-

justed models were "not statistically valid owing to a high proportion of missing data" (p. 7). This admission reveals a critical flaw in trial execution rather than validating the "optimised" result; it suggests the primary claim relies on a model that achieved statistical significance, while models accounting for known risk factors did not.

The internal validity of the trial is further threatened by the lack of a placebo control. The study was single-blind, meaning patients were aware of their treatment allocation (p. 2). The primary endpoint, incidence of heart failure, is defined partly by clinical symptoms such as dyspnea that necessitate a hospital visit (p. 3). In an unblinded trial of a novel "stem cell" therapy, patients in the intervention arm may experience a placebo effect or have a higher threshold for reporting symptoms compared to those in the standard care arm. This bias is difficult to quantify but is particularly concerning given the subjective nature of the decision to seek care. Additionally, the trial suffered from differential attrition, with a higher rate of consent withdrawal in the control group (p. 6). This imbalance suggests potential disappointment bias among controls, which undermines the randomization and complicates the interpretation of the results.

Despite these significant limitations regarding the clinical endpoints, the study offers more credible evidence regarding physiological parameters. The improvement in LVEF was assessed using echocardiography with blinded adjudication, which offers some protection against the biases affecting the patient-reported outcomes (p. 4). The observed improvement of roughly 6% in ejection fraction (p. 8) aligns with the authors' hypothesis of cardiac repair, even if the translation of this physiological change into the claimed reduction in clinical heart failure events remains statistically fragile. The study also contributes safety data for WJ-MSCs, reporting no adverse events related to tumor formation or arrhythmias (p. 8), although the precision of the efficacy estimates is limited by the low number of events—only 9 heart failure incidents occurred in the intervention group (p. 7). Ultimately, while the study

demonstrates a potential physiological signal, the claim of preventing clinical heart failure is not robustly supported by the data presented.

The Bottom Line

The claim that mesenchymal stem cell infusion significantly reduces the incidence of heart failure is not credible based on the evidence provided. The statistically significant result depends on a specific, simplified model and vanishes when adjusting for standard clinical risk factors. Furthermore, the lack of a placebo control for a symptom-driven endpoint introduces a high risk of bias. The study does, however, provide credible evidence that the therapy may improve heart function (ejection fraction) and appears safe, suggesting physiological activity that warrants further, more rigorous investigation.

Potential Issues

Fragility of the primary conclusion due to a data-driven statistical analysis: The study's central claim—that intracoronary infusion of mesenchymal stem cells reduces the incidence of heart failure—appears to be fragile and dependent on the statistical model chosen. The authors present a crude model and a final "optimised" model, both of which show a statistically significant effect (pp. 1, 9). However, the "optimised" model was derived using a backward stepwise elimination procedure, a data-driven method known to produce biased estimates and inflate statistical significance (p. 5). More robust, pre-planned analyses that adjusted for a fuller set of clinically relevant confounders are presented in the supplementary materials and show that the treatment effect is not statistically significant. For instance, a model adjusting for age, sex, baseline ejection fraction, smoking, and obesity (Model 3) yielded a non-significant result (Hazard Ratio 0.58, 95% CI 0.27 to 1.23, $p = 0.158$), as did a model that further adjusted for comorbidities (Model 4, $p = 0.117$) (Supplementary p. 30). The authors justify their preference for the simpler model by stating that the more complex models were "not statistically valid owing to a high proportion of missing data and an insufficient event-to-covariate ratio" (p. 7). While this highlights potential issues with data collection or power, it does not resolve the concern that the primary conclusion is based on a simplified model that achieved statistical significance, while more comprehensive models failed to confirm the finding.

Lack of patient blinding for a subjective primary endpoint: The trial was single-blinded, meaning patients were aware of their treatment allocation. This presents a significant threat to the internal validity of the study, as the primary endpoint, "incidence of heart failure," is based on clinical symptoms like dyspnea that lead a patient to seek care (p. 3). Patients who know they have received a novel regenerative therapy may be less likely to report symptoms or may have a higher threshold for seeking medical attention compared to those in the control group, a phenomenon related to

the placebo effect. This could lead to an under-ascertainment of heart failure events in the intervention group. The authors acknowledge this limitation, noting that ethical committee restrictions prevented a sham procedure (pp. 3, 12, Supplementary p. 11). While they employed blinded adjudicators to confirm outcomes, this strategy cannot correct for potential bias at the initial stage of symptom reporting and care-seeking, which is driven by unblinded patients and their clinicians.

Potential for bias from differential attrition: The study experienced a higher rate of participant withdrawal in the control group than in the intervention group, which may have introduced selection bias. After randomization, 20 patients (7.1%) were excluded from the control arm analysis, compared to only 4 patients (2.9%) from the intervention arm (pp. 5–6). A large portion of this difference was due to 17 control patients declining to continue after randomization, compared to only 3 in the intervention group (p. 6). In an unblinded trial, such differential attrition can be a sign of patient disappointment with their allocation, and if these patients differ systematically from those who remained, the randomization is compromised. The analysis was conducted on a modified intention-to-treat basis, including only patients who completed at least one follow-up visit, but the potential impact of this imbalanced dropout on the results was not explored with sensitivity analyses (p. 4).

Disconnect between sample size justification and final analysis: There appears to be a contradiction between the study's planned analytical strategy and the one ultimately used to support its main conclusion. The authors state that they increased the sample size specifically "To ensure adequate statistical power to enable adjustment for at least three to five covariates" (p. 3). This implies an intention to conduct a robust, multivariable-adjusted analysis. However, the final "optimised" model presented in the main text as evidence for the primary endpoint adjusts for only a single covariate (sex) (p. 9). The more comprehensively adjusted models, which were the stated goal of the sample size increase, were the same ones that yielded non-significant results and were relegated to the supplement. This suggests a potential

discrepancy between the stated analytical plan, which aimed for a robust multivariable analysis, and the final model presented as the primary evidence.

Limited generalizability due to age restrictions: The study's findings may not be generalizable to the broader population of patients who suffer myocardial infarctions, as the trial excluded individuals over the age of 65 (p. 2). Heart failure is most prevalent in older adults, who often have more comorbidities and may respond differently to therapy. By focusing on a younger cohort (mean age ~58 years), the study population is likely healthier and may have a greater capacity for cardiac repair than the typical real-world patient. The authors clearly state the age criteria, but this design choice significantly restricts the external validity of the conclusions.

Imprecision of the treatment effect estimate: The study's positive conclusions for the primary and key composite endpoints are based on a small absolute number of events in the intervention group. For both the incidence of heart failure and the composite of cardiovascular mortality and readmission, there were only 9 events in the intervention arm (p. 7). While the effect size was large enough to achieve statistical significance, the small event count means the hazard ratio estimates have low precision and are potentially unstable. A change of just a few events in the intervention group could have substantially altered the results and their statistical significance, suggesting the findings may be less robust than implied.

Inadequate handling of missing data: The analysis may be biased due to a high proportion of missing data for important baseline confounders. For example, smoking status was missing for approximately 13% of the cohort, and BMI was missing for 18% (p. 6). The authors' approach to this problem was to exclude these variables from their preferred models, citing the missing data as a reason the models were "not statistically valid" (p. 7). This is effectively a complete-case analysis, which can introduce bias if the data are not missing completely at random. The statistical methods section does not describe more robust approaches, such as multiple imputation, which are standard for handling missing covariate data (pp. 4–5).

Over-interpretation of subgroup analysis by sex: The paper speculates on a "potential sex specific benefit" of the therapy, suggesting the treatment effect was more substantial in female patients (p. 11). This conclusion appears to be an over-interpretation of an underpowered, exploratory analysis. The finding is based on a very small number of female patients in the intervention group (n=21), leading to a highly imprecise estimate with a wide confidence interval (Hazard Ratio 0.38, 95% CI 0.05 to 2.83) that is not statistically significant ($p = 0.346$) (Supplementary p. 34). The authors do appropriately caution that the findings are exploratory and require further investigation, but the prominence given to this observation in the discussion may be unwarranted given the weakness of the statistical evidence.

Presentation and clerical issues: Several minor inconsistencies and errors in the presentation of data may cause confusion for the reader. The CONSORT flow diagram is difficult to reconcile, with ambiguous labels ("Lost to 3 year follow-up" for patients who withdrew early) and numbers that do not sum correctly without reference to the main text (p. 5). The supplementary materials contain a minor arithmetic error in the description of the sample size calculation, stating that 220 plus 118 totals 328, when the correct sum is 338 (Supplementary p. 12). Finally, several reported values, including annual incidence rates for heart failure (p. 7) and the mean change in LVEF (p. 10), are not precisely reproducible from the rounded summary data provided in the tables, likely due to rounding artifacts.

Future Research

Sham-controlled trial designs: Future investigations must implement a double-blind design utilizing a sham procedure for the control group. Given that heart failure incidence relies heavily on patient-reported symptoms and the decision to seek emergency care, blinding the participant is the only way to disentangle the physiological effects of the stem cells from the psychological effects of receiving a novel therapy.

Robust data handling and imputation: To address the fragility observed in this study's statistical modeling, future trials should employ rigorous data collection strategies to minimize missingness for key covariates like BMI and smoking status. Analysis plans should pre-specify the use of multiple imputation techniques rather than excluding variables or relying on complete-case analysis, ensuring that multivariable models remain valid and powered to adjust for confounders.

Investigation of sex-specific responses: Future work should explicitly power trials to test the hypothesis that female patients derive greater benefit from this therapy. The exploratory interaction noted in this study suggests a strong sex-based differential, but the small number of female participants rendered the finding inconclusive. A stratified trial design could confirm whether this observation represents a true biological difference in response to mesenchymal stem cell therapy.

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