A Review of "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

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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.
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> 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.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

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Abstract Summary: This phase 3 randomized clinical trial assessed whether intracoronary infusion of Wharton's jelly derived mesenchymal stem cells (WJ-MSCs) reduced the incidence of post-myocardial infarction heart failure and related hospital admissions compared to standard care. The intervention significantly reduced the risk of heart failure incidence, readmission to hospital for heart failure, and improved left ventricular ejection fraction.

Key Methodology: Phase 3 randomised, single-blinded clinical trial (1:2 allocation) comparing intracoronary infusion of allogenic Wharton's jelly derived mesenchymal stem cells (WJ-MSCs) versus standard care in 396 patients with STEMI and LVEF <40%, followed up for a median of 33.2 months.

Research Question: Does intracoronary infusion of mesenchymal stem cells reduce the incidence of post-myocardial infarction heart failure compared to standard care?

Summary

Is It Credible?

The PREVENT-TAHA8 trial presents a superficially compelling case for the use of Wharton's jelly derived mesenchymal stem cells (WJ-MSCs) in preventing heart failure following acute myocardial infarction. On the surface, the results appear robust: a hazard ratio of 0.43 for the primary endpoint of heart failure incidence suggests a dramatic therapeutic benefit. However, a closer examination of the study design reveals a critical vulnerability that undermines the certainty of this conclusion. While the authors position this intervention as a "valuable adjunctive procedure," the evidence provided is insufficient to disentangle the physiological effects of the stem cells from the psychological effects of the unblinded trial design. The study succeeds in demonstrating a biological signal, particularly regarding ejection fraction, but it falls short of proving clinical efficacy in preventing heart failure events.

The central flaw lies in the absence of a sham control. The authors acknowledge that ethical constraints prevented a double-blind design, resulting in a single-blind trial where patients were aware of their treatment allocation. This is problematic because the primary endpoint—incidence of heart failure—relies heavily on patient-reported symptoms. The definition of the endpoint includes "symptoms of dyspnoea… necessitating an outpatient visit… or emergency department visit" (p. 3). In an unblinded trial, patients receiving a novel, high-tech stem cell infusion may be less likely to report mild symptoms or seek care due to a placebo effect (expectation of benefit), while control patients receiving standard care might be more hyper-vigilant or anxious, leading to a nocebo effect. Although the adjudication of events was blinded, the initial trigger for those events—the patient presenting for care—was not. Consequently, the substantial reduction in heart failure incidence may be partly or largely an artifact of patient behavior rather than physiological improvement.

This fragility is further exposed by the statistical analysis. The reported hazard ratio of 0.43 is impressive, but it is derived from an "optimised" model. When the researchers adjusted for a more comprehensive set of covariates, including smoking and obesity (Model 4), the statistical significance of the treatment effect vanished ($p = 0.117$). The authors defend this

by citing missing data and an insufficient event-to-covariate ratio, which are valid statistical concerns. Yet, the fact remains that the treatment effect is not robust enough to survive adjustment for standard cardiovascular risk factors. If the intervention were truly as potent as the unadjusted numbers suggest, one would expect the signal to persist even in an over-parameterized model. The loss of significance indicates that the observed benefit is sensitive to model specification and potential confounders.

The study also suffers from differential attrition, a common consequence of unblinded designs. The control group experienced a higher rate of dropouts and withdrawals compared to the intervention group. This introduces attrition bias, as the patients who remained in the control arm might differ systematically from those who left, potentially skewing the comparison. Furthermore, there are inconsistencies in the reporting of baseline characteristics for the physiological analysis. The baseline left ventricular ejection fraction (LVEF) means in the paired analysis match the full cohort means exactly, implying that the "improvement" analysis compares the baseline of the whole group against the follow-up of only the survivors. While the LVEF improvement in the intervention group (approximately 14 percent) appears superior to the control group (approximately 8 percent), the methodological looseness in defining the analysis populations clouds the precision of this finding.

Ultimately, PREVENT-TAHA8 contributes a promising but inconclusive chapter to the field of cardiac regenerative therapy. It confirms that intracoronary infusion of WJ-MSCs is feasible and likely has a positive effect on cardiac structure, as evidenced by the LVEF data. However, the claim that it prevents clinical heart failure is not definitively supported by the evidence. The limitations of the open-label design, combined with the statistical instability of the primary endpoint, mean that we cannot rule out the possibility that the observed clinical benefit is driven by performance bias and confounding. The study highlights the extreme difficulty of proving efficacy in this domain without a sham control, leaving the true clinical value of the intervention uncertain.

The Bottom Line

The PREVENT-TAHA8 trial suggests that stem cell therapy may improve heart function after a heart attack, but it fails to definitively prove that it prevents heart failure. The study was not double-blinded, meaning patients knew whether they received the treatment. This introduces a significant risk that the reported reduction in heart failure symptoms was influenced by the placebo effect rather than the treatment itself. Furthermore, the statistical strength of the main result disappeared when researchers adjusted for factors like smoking and obesity. While the therapy shows promise in improving heart measurements, the evidence is too fragile to confirm it as a reliable clinical solution for preventing heart failure.

Specific Issues

Lack of sham control and patient blinding: The most significant limitation of the study is the absence of a sham control, which resulted in an open-label design regarding patient awareness. The authors acknowledge that ethical committees deemed a sham procedure "ethically unacceptable" (Supplementary Materials, p. 25). However, the primary endpoint of heart failure incidence is partially subjective, relying on patients to report "symptoms of dyspnoea" and seek care (p. 3). Knowledge of treatment allocation introduces a high risk of performance bias, where intervention patients may under-report symptoms (placebo effect) and control patients may over-report them (nocebo effect). While outcome adjudication was blinded, this does not mitigate the bias inherent in the patient's decision to present for medical attention.

Statistical instability in adjusted models: The robustness of the primary conclusion is questionable due to the loss of statistical significance in fully adjusted models. While the "optimised" model showed a significant hazard ratio, Model 4, which adjusted for relevant comorbidities including smoking and obesity, showed a non-significant hazard ratio of 0.49 ($p = 0.117$) for heart failure incidence (Supplementary Materials, p. 44). The authors attribute this to missing data and limited power (p. 7), but the inability of the effect to withstand adjustment for standard risk factors suggests the finding is fragile and potentially confounded.

Differential attrition and missing data: There is evidence of differential attrition, with a higher number of withdrawals and dropouts in the control group (20 patients) compared to the intervention group (4 patients) (p. 5). This is typical in unblinded trials where control patients may lose motivation. Additionally, baseline data for key confounders like smoking and BMI showed differential missingness (Supplementary Materials, p. 33). This imbalance complicates the intention-to-treat analysis and introduces potential attrition bias that favors the intervention.

Inconsistent LVEF baseline comparison: The analysis of Left Ventricular Ejection Fraction (LVEF) change appears to use incomparable populations. The "Baseline" LVEF means re-

ported in the paired analysis table (Supplementary Materials, p. 56) are identical to the baseline means of the entire randomized cohort (p. 6), while the "6-month" means presumably include only survivors. Calculating the change by comparing the full cohort baseline to the survivor follow-up is methodologically flawed. Additionally, there is a minor arithmetic discrepancy where the reported mean change does not exactly equal the difference between the reported baseline and follow-up means (Supplementary Materials, p. 56).

Presentation and clerical errors: The text contains several clerical errors that reflect a lack of precision in reporting. The authors state "No adverse events were noticed" (p. 8), which contradicts Table 2 reporting multiple deaths and readmissions (p. 7). There is a discrepancy in the 3-year cumulative probability of HF incidence for the intervention group, reported as 5.74 percent in Table 2 (p. 7) but 7.42 percent in Supplementary Table C (Supplementary Materials, p. 40). The annual incidence rates in Table 2 do not match the result of dividing events by person-years (e.g., 9/314.47 is 2.86 percent, not 2.77 percent) (p. 7). The sample size calculation sums 220 and 118 to 328, rather than 338 (Supplementary Materials, p. 26). Finally, a hazard ratio in Supplementary Table B is reported as 0.01820, which is clearly a typo given the confidence interval (Supplementary Materials, p. 38).

Non-standard terminology in CONSORT diagram: The CONSORT diagram labels patients who declined further participation as "Lost to 3 year follow-up" (p. 5). The text clarifies that these patients explicitly declined to continue (p. 6). Labeling active withdrawals as "lost to follow-up" is misleading regarding the nature of the missing data.

Exploratory nature of sex-specific findings: The authors claim a "potential sex specific benefit" for females (p. 11), but this finding is statistically unsupported. The interaction analysis was exploratory, and the confidence intervals were extremely wide (Supplementary Materials, p. 48). The authors correctly acknowledge this as limited by sample size (p. 11), but the finding remains speculative.

Future Research

Implementation of objective primary endpoints: Future trials must circumvent the limitations of unblinded designs by selecting primary endpoints that are impervious to placebo effects. Instead of relying on symptom-driven heart failure incidence, researchers should prioritize hard, objective outcomes such as total mortality (requiring larger sample sizes) or purely physiological measures like cardiac MRI-derived volumes and scar mass, provided these are adjudicated by blinded experts. If a clinical endpoint is required in an unblinded setting, it should be defined strictly by objective biomarkers (e.g., NT-proBNP levels exceeding a threshold) rather than patient-reported dyspnea.

Robust handling of covariates and missing data: To address the statistical fragility observed in this study, future research must be powered sufficiently to allow for full adjustment of relevant covariates without losing statistical validity. Protocols must include rigorous data collection strategies to minimize missingness for key variables like smoking and BMI. Furthermore, statistical analysis plans should pre-specify sensitivity analyses that account for differential attrition, such as worst-case scenario imputation, to ensure that the treatment effect is not an artifact of control group dropout.

Matched-pair analysis transparency: Future reporting of physiological changes, such as LVEF, must ensure that baseline and follow-up comparisons are conducted on the exact same set of patients. Reporting should explicitly present the baseline characteristics of the "completer" population separately from the "intention-to-treat" population to allow for accurate assessment of change over time and to detect if the surviving cohort differs systematically from the original randomized sample.

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