Prevention of Acute Myocardial Infarction Induced Heart Failure by Intracoronary Infusion of Mesenchymal Stem Cells: A Phase III Randomized Clinical Trial (PREVENT-TAHA8)

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Background and Rationale

Myocardial Infarction and Heart Failure

Myocardial infarction (MI) represents a leading cause of mortality worldwide (1). With a reduction in the rate of mortality due to MIs in recent decades, the incidence of heart failure (HF) has been on the rise (2). This incidence ranges between 14 and 36% among those hospitalized due to an acute MI (AMI) (3). HF exerts a considerable effect on healthcare systems in America, accounting for 6 million cases, 300,000 deaths, and roughly 40 billion USD worth of costs every year (4).

Despite the therapeutic efforts (5), post-MI HF still leads to a high rate of morbidities and mortalities (6, 7). Although we have been successful in prolonging the life of HF patients and relieving symptoms, we are yet to regenerate the infarcted cardiac tissues. Hence, a gap exists in the literature as restoring the standard histological architecture of the heart should theoretically lead to improved outcomes for patients with MI-induced HF (8). This may be possible using stem cell-based therapies (9).

Cell-based therapy in cardiovascular disease

Toward the close of the 20th century, scientists signaled a new era in cardiovascular disease treatment through preclinical investigations in which skeletal myoblasts (10) and fetal cardiomyocytes (11) were transplanted into ischemic myocardium. Afterward, the intracardiac implantation of bone marrow (BM) cells were assessed in murine MI models (12, 13). Human studies commenced following the turn of the century, with skeletal myoblasts being used in HF patients in 2001 (14) and BM cells being used for AMI patients in 2002 (15). From then on, numerous investigations have aimed to amend the cardiovascular damage caused by diseases like MI and cardiomyopathy through the use of different cell-based therapies.

Mesenchymal stem cells (MSCs)

The BM, heart, Wharton's jelly, and adipose tissue are among the prime sources of MSCs (16-18). MSCs offer ease of isolation, *ex vivo* growth, in vitro proliferation, and immune-privileged properties, which is why their use in clinical trials is expanding rapidly (19). According to the POSEIDON clinical trial on MSC transplantation, allogeneic MSCs are safe and as effective as autologous MSCs (20). Notably, the TAC-HFT trial revealed the two-fold effectiveness of MSCs relative to BM-derived mononuclear cells (BM-MNCs) (21). Accordingly, MSCs appear to be an excellent candidate for cardiac regeneration trials. Few studies have used MSCs from Wharton's jelly but the results from both clinical and preclinical studies for this resource are promising. (22)

Cell-based therapy in acute myocardial infarction (AMI)

To date, BM-MNCs have been used in the majority of research on cell-based therapy following AMI. The TIME trials established that the optimal time for cell implantation following AMI is within 3-7 days (23, 24). Fisher et a., in a meta-analysis, proved that BM-MNCs augment the left ventricular ejection fraction (LVEF) following AMI by roughly 2.72%, yielding benefits both in terms of survival and function in AMI patients younger than 55 years of age with LVEF < 37% (25).

Trials involving the use of MSCs in patients following AMI have shown promising yet controversial results. Gao and coworkers conducted the largest clinical trial in this regard with 116 patients, demonstrating that umbilical cord-derived Wharton's jelly MSCs (WJ-MSCs) led to an almost five percent improvement in the LVEF (26). This figure was also confirmed in a meta-analysis for those who receive the cells in the first 10 days after AMI with an improvement around at 5.74% (27). These are in agreement with the findings of the TAC-HFT trial, which indicated the roughly two-fold effectiveness of MSCs relative to BM-MNCs (21). Also a head to head comparison of BM-MNCs with

MSCs in a meta-analysis showed similar findings (BM-MNC= 3.07%, vs MSCs = 5.65%,)(28).

BAMI trial

For over two decades, autologous cell-based treatments have been assessed in managing cardiovascular diseases through preclinical and clinical studies. However, phase III trials have been infrequent. Furthermore, the phase II trials have involved different methodologies in terms of the type of stem cells and the method and timing of delivery.

The BAMI trial was the first phase III trial conducted to clarify whether or not post-MI intracoronary transplantation of BM-MNCs would reduce all-cause mortality. Although the trial was designed to involve 3000 patients, it was stopped prematurely after the enrollment of 375 patients. Among them, 185 received BM-MNCs (intracoronary infusion) 2–8 days following primary percutaneous coronary intervention (PPCI), and the remaining 190 patients received optimal medical therapy as the control group. All-cause mortality after two years was 3.26% [n=6; 95% confidence interval (CI): 1.48–7.12%] with BM-MNCs compared to 3.82% (n=7; 95% CI: 1.84–7.84%) with optimal medical therapy. The main reason behind such results was that mortality was much lower than expected at the time of study design. At the start of the project in 2011, the literature held that following an AMI, the mortality rate from all causes after two years would be approximately 12% among those with an LVEF ≤ 45% post-reperfusion therapy (3). However, the researchers noticed a 3.85% mortality rate while conducting the study, reflecting the evolution of primary angioplasty procedures in those years. Importantly, the investigators noticed that only five patients (2.7%, 95% CI: 1.0–5.9%) who received BM-MNCs were hospitalized due to HF during the two years of follow-up compared with 15 patients (8.1%, CI: 4.7–12.5%) who received optimal medical therapy (HR: 0.33, 95% CI: 0.12–0.88), representing the sole clinical benefit observed. BAMI showed

us that taking mortality as an endpoint for stem cell therapy trials may be difficult to achieve as the primary endpoint in trials with medium sample sizes and the best clinical endpoint to assess is HF incidence. In a recent meta-analysis, it was again shown that injection of BM-MNCs was associated with lower risk of composite end points of hospitalization for congestive heart failure (CHF), re-infarction, and cardiac-related mortality (91/1191 vs. 111/812, RR = 0.643, 95% CI = 0.489 to 0.845, p = 0.002). This effect was derived from both reduction of CHF (47/1220 vs. 62/841, RR = 0.568, 95% CI = 0.382 to 0.844, p = 0.005) and re-infarction rate (23/1159 vs. 30/775, RR = 0.583, 95% CI = 0.343 to 0.991, p = 0.046), but not cardiac-related mortality (28/1290 vs. 31/871, RR = 0.722, 95% CI = 0.436 to 1.197, p = 0.207).(29)

Hypothesis generation

Since the efficacy of MSCs is higher than BM-MNCs after AMI in the improvement of LVEF, it would be probable that these cells may have a better clinical effect as well.

Conclusion of Rationale

Currently, the primary focus of post-AMI treatment is to prevent remodeling and avert any further loss of myocytes (5). However, a revolution can potentially be achieved by regenerative medicine, aiming to restore cardiac function by inhibiting and even reversing the process of remodeling through the use of stem cells (26). Even though some investigations were not very promising in this regard (9), other studies have shown that stem cell therapy may be of value in certain populations.

Although a Cochrane meta-analysis revealed that the LVEF of young AMI patients does not increase following BM-MNC therapy, survival and functional benefits may be present (25). Importantly, research with MSCs has yielded more promising results, with the TAC-HFT trial indicating the roughly two-fold higher efficacy of MSCs relative to BM-MNCs (21).

According to meta-analyses of the various clinical trials, MSCs can improve the LVEF by 5.72% (27), while BM-MNCs can achieve an inferior improvement of 3.07% (28).

Currently, scientists are yet to understand the exact mechanisms behind the therapeutic impact of stem cells, especially MSCs. However, the most commonly suggested mechanism is paracrine signaling, where the implanted stem cells alter the activity of the nearby cells in the heart via mediators like cytokines (30). Also, it is still unclear whether or not the mechanical improvements in LV function after MSC transplantation would be translated into a clinical benefit by reducing major cardiovascular events. Our trial provides essential insights into the field by including selected patients who develop reduced LVEFs after AMIs.

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Protocol Summary

Study Setting and Design

This randomized, multicenter, single-blinded phase III clinical trial aims to assess whether intracoronary infusion of umbilical cord Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) provides a superior effect in reducing the incidence of heart failure (HF) following acute myocardial infarctions (AMIs) compared to standard treatment. The study protocol has been approved by the Ethics Committee of Shiraz University of Medical Sciences (Approval Code: IR.SUMS.REC.1400.409), and the trial is registered on ClinicalTrials.gov under the identifier NCT05043610.

The trial involves three percutaneous coronary intervention (PCI)-capable centers located in Shiraz, Iran, including Alzahra Heart Hospital, Faghihi Hospital, and Namazi Hospital. These centers are coordinated through Alzahra Heart Center, where the randomization process is centrally managed. However, interventions and patient care are conducted at their respective centers.

Randomization was performed using permuted block randomization with a block size of six, implemented through a web-based service (https://www.sealedenvelope.com/randomisation/simulation/). A 2:1 allocation ratio (control to intervention) was chosen to minimize potential risks associated with the novel therapy, optimize statistical power, and provide a larger control group for more robust comparisons.

Participants were randomized into two groups, with one group receiving intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) in addition to standard therapy, while the control group received standard therapy alone.

In the PREVENT-TAHA8 trial, patient blinding was not feasible due to the inability to implement a sham procedure for the intervention. (The initial study design included a sham procedure for the control group to enhance blinding and minimize potential bias. However, the local ethical committee deemed the sham procedure ethically unacceptable due to its invasive nature and required its removal from the study protocol. Consequently, the final study design was modified to exclude the sham procedure, ensuring compliance with ethical guidelines while maintaining the scientific integrity of the trial. Similarly, the physician administering the intracoronary WJ-MSC infusion was not blinded; however, this individual had no involvement in patient follow-up, outcome assessment, or post-procedural care to prevent potential bias.

To ensure the integrity of outcome evaluation, all outcome assessors and data analysts remained blinded to treatment allocation until the conclusion of the study, thereby maintaining a single-blind study design.

Eligibility Criteria

Inclusion Criteria:

Participants must meet the following criteria to be eligible for the study:

1. Age: 18 to 65 years
2. Gender: Both male and female participants are eligible

3. Recent Myocardial Infarction (MI): First MI occurring within the preceding 3 to 7 days
4. Left Ventricular Ejection Fraction (LVEF): Post-acute myocardial infarction (AMI) LVEF < 40%
5. Pregnancy Status: Negative pregnancy test required for women of reproductive age
6. Consent: Provision of written informed consent

Exclusion Criteria:

Participants will be excluded if any of the following conditions are present:

1. Pre-existing Cardiac Conditions: History of valvular, ischemic, or congenital heart disease
2. Regional Wall Motion Abnormalities: Abnormalities outside the infarcted region
3. Left Ventricular Dysfunction from Non-Ischemic Causes:
    - Non-ischemic cardiomyopathy
    - History of anthracycline use
    - Chronic ethanol abuse (>6 oz/day regularly)
4. Echocardiographic Limitations: Poor echocardiographic imaging window
5. Significant Comorbidities: Presence of active infection, malignancy, or autoimmune disease

Sample Size Calculation

The primary outcome of this study is to compare the incidence of heart failure (HF) between the intervention and control groups. Based on data from the BAMI trial, which reported a one-year incidence rate of 1.3% and 4%, it is projected that, over a three-year follow-up period, the incidence rate will be 3.9% in the intervention group and 12% in the control group.

Given that the intervention involves umbilical cord Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs), which remain an experimental therapy, a 2:1 randomization ratio (control to intervention) was chosen. This approach enhances statistical efficiency, ethical considerations, cost-effectiveness, and feasibility, making it a strategic choice for evaluating the efficacy of WJ-MSC therapy.

Using the following formula:

$$n = \frac{(1+R)}{R} P(1-P)\left(t_{\alpha,v} + t_{\beta(1),v}\right)^2 / (\Delta)^2$$

Where:

- R = 2 (allocation ratio: 2 control participants per 1 intervention participant),
- P represents the weighted average incidence rate across groups,
- $t_{\alpha,v}$ =1.96 (for a 5% significance level, two-tailed),
- $t_{\beta(1),v}$ = 0.84 (for 80% power),
- Δ represents the absolute difference in HF incidence between groups,

the required sample size was calculated as 220 participants in the control group and 118 in the intervention group, totaling 328 participants.

To ensure adequate statistical power to enable the adjustment for at least 3–5 covariates, a minimum of 30–40 HF events was required in the total population. To accommodate this and enhance the robustness and reliability of the treatment effect estimation, the sample size was increased to 390 participants.

Additionally, considering the novelty of the intervention and the logistical challenge of a 3–7 day gap between primary percutaneous coronary intervention (PCI) and intracoronary infusion of WJ-MSCs, an 8% consent withdrawal rate was anticipated. To compensate for potential dropouts, the final recruitment target was set at 420 participants, maintaining a 1:2 intervention-to-control allocation ratio.

Randomisation and Blinding

Randomisation was performed using permuted block randomisation via a secure web-based platform (https://www.sealedenvelope.com/randomisation/simulation/), with a fixed block size of six. Participants were allocated in a 2:1 ratio into two groups: one group received intracoronary infusion of Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) in addition to standard therapy, while the control group received standard therapy alone. Outcome assessors remained blinded to group allocation throughout the study (single-blind design).

Intervention

This study utilized current Good Manufacturing Practice (cGMP)-certified, clinical-grade human Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs), supplied by Cell Tech Pharmed Co. Ltd., Tehran, Iran. The WJ-MSCs were transported to the hospital on the same day as the infusion and suspended in normal saline (0.9%). Each batch was analyzed and certified by a qualified specialist to ensure compliance with product specifications. Standard operating procedures (SOPs) were strictly followed during shipment and handling.

Procedure

Patients in the intervention group were taken to the cardiac catheterization laboratory, where the intracoronary infusion of 10^7 WJ-MSCs was performed. A weight-based bolus dose of heparin was administered to patients with an activated clotting time below 200 seconds before the procedure.

For catheterization, a 6 Fr therapeutic guiding catheter was inserted into the left coronary artery. After infusion of nitroglycerin (200 μg) through the catheter, the left anterior descending (LAD) artery was assessed, and the Thrombolysis in Myocardial Infarction (TIMI) flow was documented. A 0.014-inch soft-tipped guidewire was placed at the distal edge of the stent in the LAD. Next, an over-the-wire balloon was advanced to the stented area, where it was inflated to achieve occlusion. Following the removal of the guidewire, the infusion catheter was connected to an infusion syringe containing WJ-MSCs.

The WJ-MSCs were infused at a rate of 2.5 ml/min, with a total infusion volume of 7.5 cc. To maintain occlusion, low-pressure inflation (2–4 bar) of the balloon catheter was applied, ensuring complete coronary occlusion before infusion, which will be confirmed using contrast dye.

The infusion process was conducted in three stages:

1. After each one-third of the cell infusion, the process was paused.
2. TIMI coronary flow was assessed using a contrast agent before resuming the infusion.
3. Once the entire volume has been infused, a coronary flow wire was placed via the microinfusion catheter.

No specific adherence measures were required for this intervention, as it was a one-time treatment with no need for continued patient compliance.

Follow-Up and Patient Care

All patients in both the control and intervention groups received guideline-directed medical therapy (GDMT) for acute myocardial infarction (AMI), which includes:

- Aspirin
- Ticagrelor
- Rosuvastatin
- Valsartan
- Bisoprolol
- Additional therapies such as eplerenone and implantable cardioverter-defibrillator (ICD) insertion were considered based on individual patient conditions.

During hospitalization, patients received daily visits from a cardiologist, and all physical examination findings were recorded. Patients were closely monitored for early manifestations of complications, including:

- Arrhythmias
- Pulmonary embolism
- Coronary artery injury

Additionally, an electrocardiogram (ECG) was obtained for cardiac evaluation.

Baseline and Post-Intervention Assessment

Prior to MSC infusion, a comprehensive cardiac evaluation was performed, including echocardiography to determine the initial ejection fraction (EF), calculated using the wall motion score and Simpson's rule.

Once the MSC infusion is completed and the patient is hemodynamically stable, the following medications were prescribed for home use:

- Beta-blockers
- Angiotensin-converting enzyme (ACE) inhibitors
- Aldosterone antagonists
- Aspirin
- Ticagrelor
- Statins
- Glyceryl trinitrate (spray or tablets)

All patients were also enrolled in a cardiac rehabilitation program.

Follow-Up Protocol

First follow-up visit: 10 days after discharge

Subsequent visits: Every three months

Echocardiography assessments: At six months

Study Endpoints (Outcome Definitions)

Primary Endpoint:

- Incidence of heart failure (HF)
    - HF is defined as a condition requiring hospitalization (with related ICD-9 or ICD-10 code mentioned below) or an emergency department (ED) visit where infusion therapy is administered to treat a clinical syndrome associated with multiple signs and symptoms indicative of cardiac decompensation or impaired heart pump function. The adjudication process will follow the ARIC study adjudication system. The incidence of HF will include both definite and possible cases of acute decompensation, covering both heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF).
    - The identification of HF should not rely solely on a single clinical indicator, such as dyspnea, edema, a low ejection fraction, or an elevated brain natriuretic peptide (BNP) level. For an ED visit alone to be classified as HF incidence, the medical record must provide clear, specific, and unequivocal documentation confirming the administration of IV therapy, regardless of the findings from the patient's history, physical examination, or other evaluations. The IV therapy administered must include either a loop diuretic or an inotropic agent.
    - Right-sided heart failure is not considered a PREVENT-TAHA8 outcome and, therefore, will not be adjudicated under this classification.
    - Signs and symptoms indicative of new or worsening heart failure may include a new onset or worsening of shortness of breath, edema, paroxysmal nocturnal dyspnea, orthopnea, or hypoxia. Additionally, physician documentation should confirm that the primary reason for hospitalization or the ED visit was heart failure.
    - Heart failure is considered unlikely in patients undergoing chronic dialysis if their symptoms are due to inadequate dialysis, with no clinical or diagnostic evidence of systolic or diastolic dysfunction or a prior history of HF. Similarly, HF is unlikely when another comorbidity, such as an exacerbation of chronic obstructive pulmonary disease (COPD), fully accounts for the acute symptoms.
    - ICD-10 Codes for Heart Failure (HF): I50.0 (Congestive HF), I50.1 (Left ventricular failure), I50.2 (Systolic HF: I50.20 [Unspecified], I50.21 [Acute], I50.22 [Chronic], I50.23 [Acute on chronic]), I50.3 (Diastolic HF: I50.30 [Unspecified], I50.31 [Acute], I50.32 [Chronic], I50.33 [Acute on chronic]), I50.4 (Combined HF: I50.40 [Unspecified], I50.41 [Acute], I50.42 [Chronic], I50.43 [Acute on chronic]), I50.8 (Other HF), I50.9 (Unspecified HF).
    - ICD-9 Codes for Heart Failure (HF) (Historical Use): 428.0 (Congestive HF), 428.1 (Left HF), 428.20 (Systolic HF: 428.21 [Acute], 428.22 [Chronic], 428.23 [Acute on chronic]), 428.30 (Diastolic HF: 428.31 [Acute], 428.32 [Chronic], 428.33 [Acute on chronic]), 428.40 (Combined HF: 428.41

[Acute], 428.42 [Chronic], 428.43 [Acute on chronic]), 428.9 (Unspecified HF).

Secondary Endpoints:

- Rehospitalisation due to HF
    - To minimize diagnostic bias, reduce the risk of misidentifying outcomes, and accurately account for rehospitalization as part of composite outcomes (related major adverse cardiovascular outcomes), we have categorized cases of rehospitalization due to heart failure (HF) separately within the HF incidence outcome. Notably, hospitalization with with related ICD-9 or ICD-10 code mentioned above is considered as definite rehospitalization due to HF. This approach allows for a more precise evaluation while ensuring that rehospitalization is recognized as a significant event alongside other related MACE, which include cardiovascular mortality and rehospitalization due to myocardial infarction (MI).
- All-Cause Mortality
    - Any death that occurs during the study period, regardless of the reported cause, and is documented in Forensic Medicine will be recorded and considered in the study outcomes.
- Cardiovascular Mortality
    - Cardiovascular (CVD) death is defined based on its temporal relationship to a documented cardiovascular event, such as hospitalization for myocardial infarction (MI) or stroke, or postmortem findings indicating an acute cardiovascular event. A definite CVD death is confirmed through these criteria, while a probable coronary heart disease (CHD) death is determined by autopsy findings showing chronic CHD, a prior history of CHD, or symptoms consistent with CHD before death, with no other identifiable cause. A possible fatal CHD case is adjudicated based on death certificate information suggesting CHD as the underlying cause, without evidence of a non-coronary explanation.
    - For hospitalized patients, definite fatal MI includes deaths occurring within 28 days of hospital admission for a confirmed MI or cases with postmortem evidence of MI within the same period. Probable fatal MI includes deaths within 28 days of admission for probable MI cases or deaths within 6 hours of admission with cardiac symptoms, where diagnostic tests (e.g., biomarkers, ECG) are absent or inconclusive. A possible fatal coronary event is classified when death occurs within 28 days of admission for conditions like possible MI, unstable angina, or chronic stable angina, or when autopsy findings reveal an old infarct or significant atherosclerosis (>50% narrowing of coronary arteries).
    - For out-of-hospital CHD deaths, definite fatal MI is confirmed if there is a history of definite or probable MI within 28 days, no evidence of a non-coronary cause, or postmortem findings of a recent MI or coronary occlusion. Definite fatal CHD includes cases with a prior history of CHD or cardiac pain within 72 hours before death, without an alternative cause, or autopsy findings showing chronic CHD (e.g., atherosclerosis, myocardial scarring). Possible

fatal CHD is classified based on ICD codes (ICD-9: 410–414, 427.5, 429.2; ICD-10: I20–I25, I46) and no evidence of a non-coronary cause.

- Other cardiovascular-related deaths include stroke-related mortality, where death follows a clinically confirmed stroke, and sudden cardiac death (SCD), occurring within one hour of symptom onset, suggesting an arrhythmic event, provided it is witnessed with no other lethal non-atherosclerotic cause. Death due to congestive heart failure (CHF) is classified when clinical, radiologic, or postmortem evidence confirms CHF as the primary cause, without signs of an acute ischemic event (including cardiogenic shock). Additionally, deaths due to ruptured aortic aneurysms, intestinal ischemia from atherosclerosis or embolic events (e.g., atrial fibrillation), or complications from attempted aneurysm repair are included under non-cardiac but other cardiovascular causes. However, pulmonary embolism, traumatic arterial ruptures, and inflammatory arteritis-related conditions are excluded.

- Rehospitalisation due to MI (Reinfarction)
  - A hospitalization is classified as MI-related if the following criteria are met:
    - Cardiac Biomarkers:
      - Diagnostic MI: At least one positive biomarker (e.g., troponin or CK-MB) with a rising or falling pattern, at least twice the upper limit of normal (ULN), in the setting of clinical cardiac ischemia and in the absence of non-cardiac causes.
    - Electrocardiographic (ECG) Evidence:
      - Evolving MI: New diagnostic Q waves or evolving major ST elevation/depression or T wave inversion.
      - Positive ECG: New left bundle branch block (LBBB), evolving ST elevation, or evolving Q wave with ST/T wave changes.
      - Nonspecific ECG Changes: Minor Q waves or ST-T changes in the absence of diagnostic biomarker elevation.
    - Cardiac Symptoms or Signs:
      - Acute chest pain, arm pain, jaw pain, neck pain, epigastric pain, or discomfort suggestive of ischemia.
      - Acute heart failure or cardiogenic shock without an alternative non-cardiac cause.
  - Classification of Rehospitalization Due to MI:
  - Definite MI Rehospitalization: Meets diagnostic biomarker, ECG, and cardiac symptom criteria.
  - ICD Codes for Myocardial Infarction (MI) and Related Rehospitalization
    - ICD-10 Codes for MI: I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22.0, I22.1, I22.8, I22.9, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24.0, I24.1, I24.8, I24.9, I25.2
    - ICD-9 Codes for MI: 410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9, 411.0, 411.1, 411.8, 412
  - Non-MI Acute Coronary Syndrome (ACS) Rehospitalization:
  - Defined as hospitalization for a new or worsening symptom pattern of coronary ischemia that does not meet MI criteria but requires evaluation for MI.

        - ICD-10 Codes for Non-MI ACS: I20.0, I20.1, I20.8, I20.9
        - ICD-9 Codes for Non-MI ACS: 411.1, 411.81
- LVEF at 6 months visit (2nd or 3rd visit post-discharge within 4-8 months post-AMI)
    - At the 6-month follow-up visit (4–8 months post-PCI for anterior LAD STEMI), left ventricular ejection fraction (LVEF) is measured using Simpson's Biplane Rule via echocardiography. This involves tracing the left ventricular endocardial border in apical 4-chamber (A4C) and apical 2-chamber (A2C) views at end-diastole and end-systole, calculating LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV), and applying the formula: LVEF (%) = [(LVEDV - LVESV) / LVEDV] × 100.
- ICD or CRT indication
    - Patients with LVEF <30% at 6 months follow-up or documented heart failure (HF) incidence with echocardiographic evidence of LVEF <35% during study period are considered for implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) based on AHA guidelines.

Composite Endpoints (The occurrence of the earliest primary or secondary endpoint will be defined as the composite outcome event.)

- Composite of cardiovascular death and rehospitalisation due to HF or MI
- Composite of all-cause death and rehospitalisation due to MI or HF
- Composite Endpoint of HF Incidence and Reinfarction (Rehospitalisation due to MI)
- Composite Endpoint of Rehospitalization due to HF or MI
- Composite Endpoint of Cardiovascular Mortality and Reinfarction (Rehospitalisation due to MI)
- Composite Endpoint of All-Cause Mortality and Incidence of HF or MI (rehospitalization due to MI)
- Composite Endpoint of Cardiovascular Mortality and Incidence of HF or MI (rehospitalization due to MI)

All patient data will be entered, encoded, and securely stored in a local database to ensure confidentiality and data integrity.

Prior to statistical analysis, all measurements underwent adjudication by an experienced cardiologist who was not part of the research team. This adjudicator assessed the quality of each measurement and excluded those deemed inadequate, which were considered as missing data in the analysis.

An independent, blinded safety committee was responsible for evaluating potential major adverse cardiac events (MACEs) to ensure objective assessment of safety outcomes.

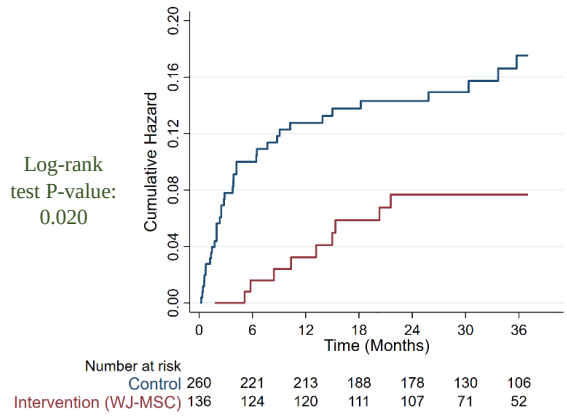
Supplementary Table A. Comprehensive Baseline Characteristics of Patients in the Prevent-TAHA8 Trial

characteristics	statistics	WJ-MSC (N=136)	Control (N=260)	Total (N=396)	P-value
Total population	N	136	260	396	
Male	n/N (%)	115/136 (84.6)	205/260 (78.8)	320/396 (80.8)	0.17
Age	[n] Mean (SD)	[136] 57.8 (10.7)	[260] 59.2 (10.9)	[396] 58.7 (10.8)	0.21
Time to intracoronary infusion	[n] Mean (SD)	[136] 5.8 (1.4)	-	-	-
Smoking	n/N (%)	73/124 (58.9)	137/222 (61.7)	210/346 (60.7)	0.60
BMI	[n] Mean [SD]	[117] 27.6 (4.8)	[208] 27.6 (4.3)	[325] 27.6 (4.4)	0.89
BMI < 25	n/N (%)	33/117 (28.2)	63/208 (30.3)	96/325 (29.5)	0.23
BMI [25-30)	n/N (%)	56/117 (47.9)	94/208 (45.2)	150/325 (46.2)	
BMI ≥ 30 (obesity)	n/N (%)	28/117 (23.9)	51/208 (24.5)	79/325 (24.3)	
Signs at admission					
Heart rate	[n] Mean (SD)	[123] 77.7 (13.6)	[222] 77.3 (12.3)	[345] 77.4 (12.7)	0.77
Systolic blood pressure	[n] Mean (SD)	[135] 116.1 (15.7)	[260] 115.4 (18.1)	[395] 115.6 (17.3)	0.33
Diastolic blood pressure	[n] Mean (SD)	[135] 71.1 (9.8)	[260] 70.4 (12.1)	[395] 70.6 (11.3)	0.25
Body temperature	[n] Mean (SD)	[108] 36.5 (0.5)	[203] 36.6 (0.5)	[311] 36.5 (0.5)	0.93
Medical history					
Hypertension	n/N (%)	57/136 (41.9)	117/260 (45.0)	174/396 (43.9)	0.55
Diabetes	n/N (%)	25/124 (20.2)	30/222 (13.5)	55/346 (15.9)	0.10
Hypercholesterolemia	n/N (%)	42/136 (30.9)	85/260 (32.7)	127/396 (32.1)	0.80
Cerebrovascular accident	n/N (%)	6/124 (4.8)	9/221 (4.1)	15/345 (4.3)	0.73
Peripheral vascular disease	n/N (%)	0/124 (0.0)	3/221 (1.4)	3/345 (0.9)	0.19
Chronic kidney disease	n/N (%)	5/124 (4.0)	5/221 (2.3)	10/345 (2.9)	0.34
Laboratory findings					
eGFR	[n] Mean (SD)	[136] 80.3 (20.1)	[260] 81.9 (19.9)	[396] 81.3 (19.9)	0.48
eGFR < 90	n/N (%)	[136] 87 (63.9)	[260] 161 (61.9)	[396] 248 (62.6)	0.68
eGFR < 60	n/N (%)	[136] 18 (13.24)	[260] 39 (15.0)	[396] 57 (14.4)	0.63
Anemia	n/N (%)	23/136 (16.9)	52/260 (20.0)	75/396 (18.9)	0.45
Echocardiographic findings					

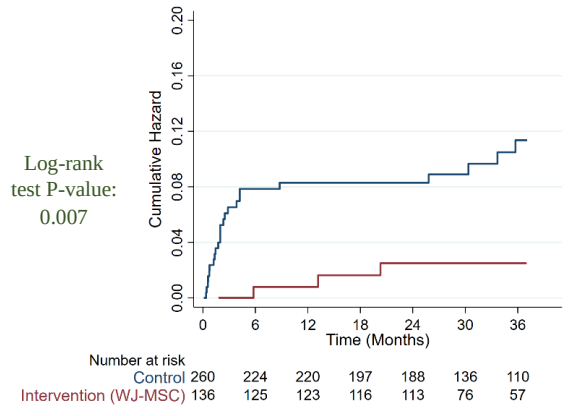
Baseline LVEF%	[n] Mean (SD)	[136] 33.0 (4.9)	[260] 33.6 (5.0)	[396] 33.4 (5.0)	0.15
LVEF < 30	n/N (%)	33/136 (24.3)	61/260 (23.5)	94/396 (23.7)	0.85
Hospital drugs					
Aspirin	n/N (%)	130/136 (95.6)	254/258 (98.4)	384/394 (97.5)	0.08
Clopidogrel	n/N (%)	35/136 (25.7)	85/259 (32.8)	120/395 (30.4)	0.14
Ticagrelor	n/N (%)	59/136 (43.4)	110/258 (42.6)	169/394 (42.9)	0.88
Beta blocker	n/N (%)	122/136 (89.7)	234/258 (90.7)	356/394 (90.4)	0.75
Morphine	n/N (%)	42/124 (33.9)	82/221 (37.1)	124/345 (35.9)	0.54
Statins	n/N (%)	127/136 (93.4)	250/258 (96.9)	377/394 (95.7)	0.10
Angiotensin receptor blocker	n/N (%)	18/136 (13.2)	20/258 (7.8)	38/394 (9.6)	0.08
Angiotensin-converting enzyme inhibitor	n/N (%)	116/136 (85.3)	215/258 (83.3)	331/394 (84.0)	0.61
Diuretic	n/N (%)	52/124 (41.9)	92/221 (41.6)	144/345 (41.7)	0.95
Anti-arrhythmic agent	n/N (%)	8/124 (6.5)	25/221 (11.3)	33/345 (9.6)	0.14
Aldosterone blockers	n/N (%)	54/136 (39.7)	95/259 (36.7)	149/395 (37.7)	0.55
Unfractionated heparin	n/N (%)	83/124 (66.9)	159/221 (71.9)	242/345 (70.1)	0.32
Low-molecular-weight heparin	n/N (%)	60/124 (48.4)	118/221 (53.4)	178/345 (51.6)	0.37

Supplementary Figure A. Cumulative Hazard Estimates and log-rank test of the PREVENT-TAHA8 trial's endpoints

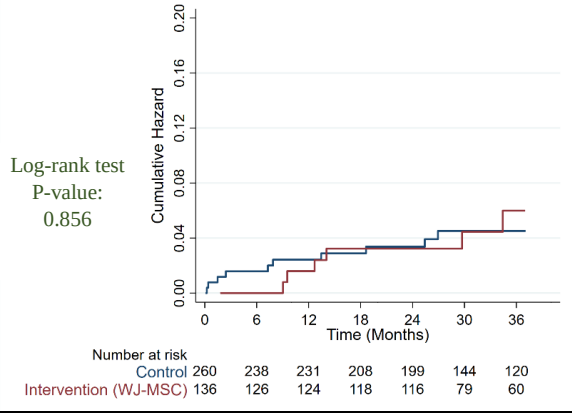
A. HF Incidence (Development)



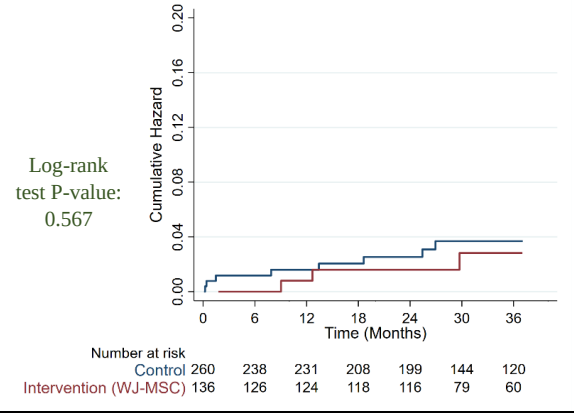
B. Rehospitalisation due to HF



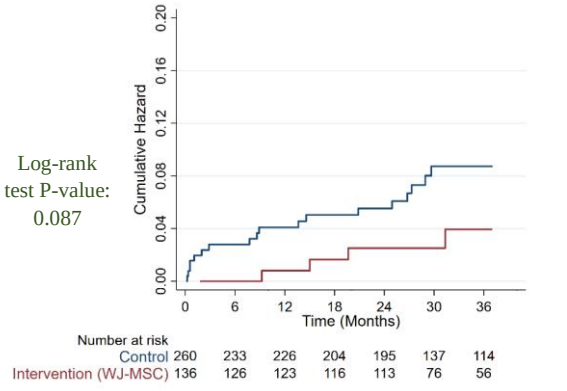
C. All-Cause Mortality



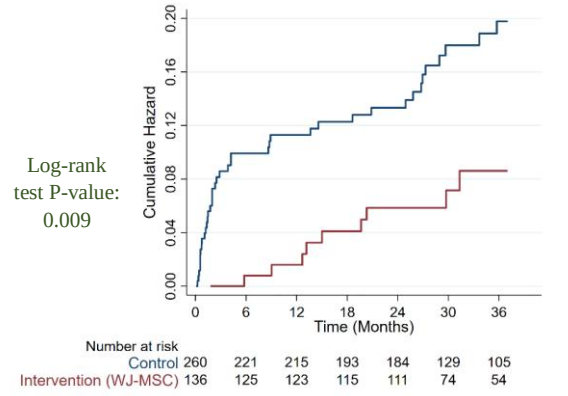
D. Cardiovascular Mortality



E. Rehospitalisation due to MI (Reinfarction)

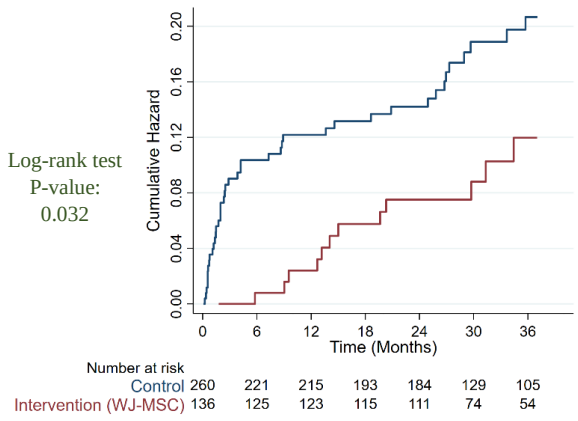


F. Composite Endpoint of Cardiovascular Mortality and Rehospitalisation due to MI or HF

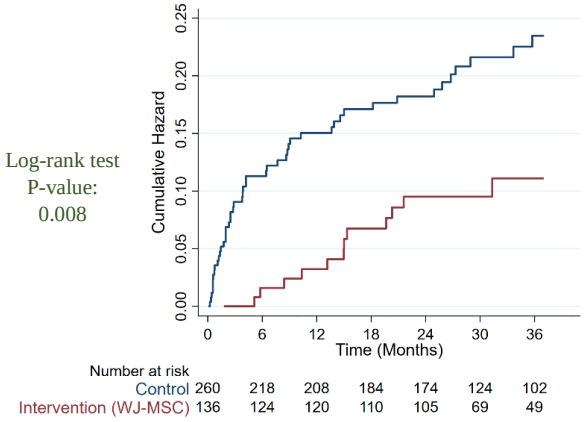


G. Composite Endpoint of All-Cause Mortality and	H. Composite Endpoint of HF Incidence

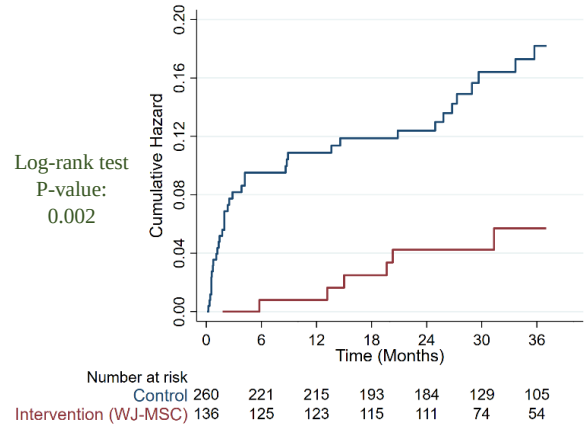
Rehospitalisation due to MI or HF



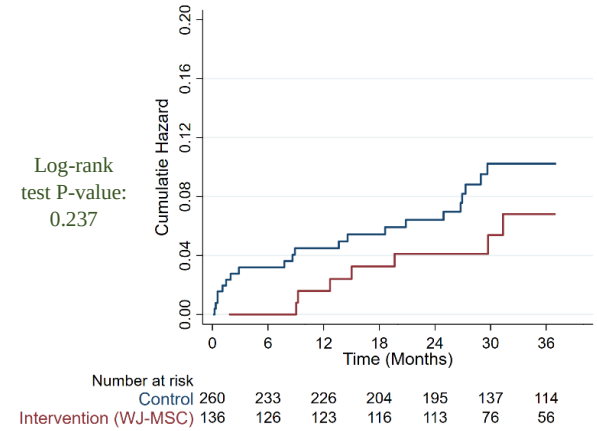
(development) and Reinfarction (Rehospitalisation due to MI)



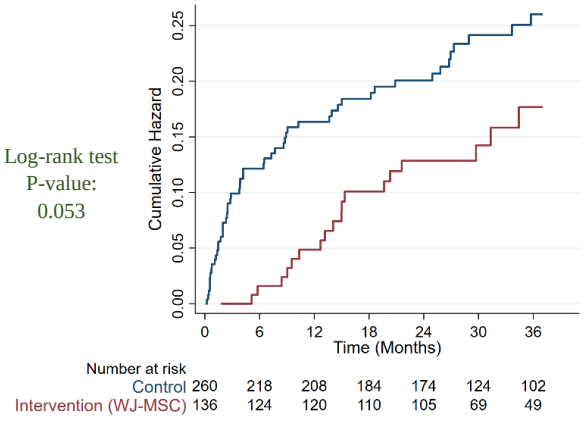
I. Composite Endpoint of Rehospitalisation due to HF or MI (Reinfarction)



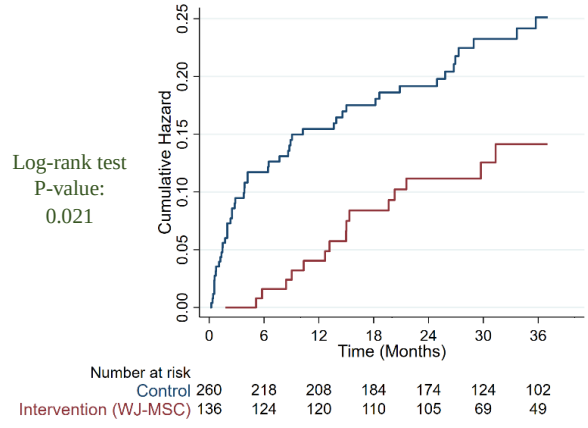
J. Composite Endpoint of Cardiovascular Mortality and Reinfarction (Rehospitalisation due to MI)



K. Composite Endpoint of All-Cause Mortality, HF Incidence, and Reinfarction (rehospitalization due to MI)



L. Composite Endpoint of Cardiovascular Mortality, HF Incidence, and Reinfarction (rehospitalization due to MI)



Subscription: A: primary endpoint - Heart Failure (HF) incidence (development). B: rehospitalization due to HF. C: all-cause mortality. D: cardiovascular mortality. E: rehospitalization due to Myocardial infarction (MI). F: composite endpoint of cardiovascular mortality and rehospitalization due to HF or MI. G: composite of all-cause death, rehospitalisation due to MI or HF. H: composite endpoint of HF incidence and reinfarction (rehospitalisation due to MI). I: composite endpoint of rehospitalization due to HF or MI. J: composite endpoint of cardiovascular mortality and reinfarction (rehospitalisation due to MI). K: composite endpoint of all-cause mortality and incidence of HF or MI (rehospitalization due to MI). M: composite endpoint of cardiovascular mortality and incidence of HF or MI (rehospitalization due to MI)

Supplementary Table B. Cumulative Hazard Ratios of Primary and Secondary Outcomes in Intervention and Control Group at 1, 2, and 3 years of follow-up

	Intervention (WJ-MSC)			Control		
	1-year	**2-year**	**3-year**	**1-year**	**2-year**	**3-year**
HF incidence (development)	0.0323 (0.0121-0.0860)	0.0768 (0.0399-0.1477)	0.0768 (0.0399-0.1477)	0.1276 (0.0891-0.1826)	0.1431 (0.1016-0.2015)	0.1753 (0.1256-0.2446)
Rehospitalisation due to HF	0.0079 (0.0011-0.0563)	0.0250 (0.0080-0.0774)	0.0250 (0.0080-0.0774)	0.0830 (0.0535-0.1287)	0.0830 (0.0535-0.1287)	0.1136 (0.0749-0.1724)
All-cause mortality	0.0159 (0.0040-0.0637)	0.0323 (0.0121-0.0862)	0.0599 (0.0261-0.1377)	0.0243 (0.0337-0.0452)	0.0337 (0.0168-0.0674)	0.0452 (0.0241-0.0846)
Cardiovascular mortality	0.0079 (0.0011-0.0563)	0.0160 (0.0040-0.0640)	0.0282 (0.0089-0.0896)	0.0160 (0.0060-0.0426)	0.0253 (0.0114-0.0566)	0.0369 (0.0183-0.0744)
Rehospitalisation due to MI	0.0080 (0.0011-0.0568)	0.0251 (0.0081-0.0779)	0.0394 (0.0143-0.1084)	0.0410 (0.0220-0.0762)	0.0553 (0.0320-0.0954)	0.0872 (0.0544-0.1400)
Composite of cardiovascular death and rehospitalisation due to HF or MI	0.0159 (0.0040-0.0637)	0.0585 (0.0279-0.1227)	0.0862 (0.0440-0.1688)	0.1129 (0.0774-0.1647)	0.1332 (0.0935-0.1896)	0.1978 (0.1434-0.2727)
Composite of all-cause death, rehospitalisation due to MI or HF	0.0240 (0.0077-0.0744)	0.0750 (0.0390-0.1442)	0.1197 (0.0663-0.2159)	0.1218 (0.0846-0.1753)	0.1420 (0.1009-0.2000)	0.2066 (0.1511-0.2826)
Composite Endpoint of HF Incidence and Reinfarction (Rehospitalisation due to MI)	0.0323 (0.0121-0.0860)	0.0951 (0.0526-0.1719)	0.1110 (0.0622-0.1982)	0.1504 (0.1079-0.2096)	0.1820 (0.1338-0.2476)	0.2348 (0.1753-0.3144)
Composite Endpoint of Rehospitalization due to HF or MI	0.0079 (0.0011-0.0563)	0.0424 (0.0176-0.1018)	0.0571 (0.0250-0.1301)	0.1088 (0.0740-0.1599)	0.1239 (0.0860-0.1785)	0.01820 (0.1302-0.2542)
Composite Endpoint of Cardiovascular Mortality and Reinfarction (Rehospitalisation due to MI)	0.0159 (0.0040-0.0637)	0.0412 (0.0171-0.0989)	0.0681 (0.0317-0.1461)	0.0449 (0.0249-0.0812)	0.0642 (0.0386-0.1067)	0.1023 (0.0661-0.1584)
Composite Endpoint of All-Cause Mortality and Incidence of HF or MI (rehospitalization due to MI)	0.0486 (0.0218-0.1082)	0.1285 (0.0774-0.2133)	0.1768 (0.1091-0.2863)	0.1635 (0.1189-0.2248)	0.2006 (0.1496-0.2691)	0.2601 (0.1971-0.3434)
Composite	0.0404	0.1116	0.1414	0.1545	0.1917	0.2512

Endpoint of Cardiovascular Mortality and Incidence of HF or MI (rehospitalization due to MI)	(0.0168-0.0971)	(0.0647-0.1923)	(0.0840-0.2377)	(0.1114-0.2144)	(0.1419-0.2588)	(0.1892-0.3334)

Supplementary Table C. Estimates Failure Rate Percentage (95%CI) of Primary and Secondary Outcomes in Intervention and Control Group at 1, 2, and 3 years of follow-up

	Intervention (WJ-MSC)			Control		
	1-year	**2-year**	**3-year**	**1-year**	**2-year**	**3-year**
HF incidence (development)	3.19 (1.21-8.27)	7.42 (3.93-13.78)	7.42 (3.93-13.78)	12.01 (8.55-16.73)	13.37 (9.69-18.30)	16.12 (11.83-21.76)
Rehospitalisation due to HF	0.79 (0.11-5.50)	2.48 (0.80-7.48)	2.48 (0.80-7.48)	7.98 (5.23-12.11)	7.98 (5.23-12.11)	10.77 (7.24-15.88)
All-cause mortality	1.59 (0.40-6.20)	3.19 (1.21-8.29)	5.85 (2.59-12.93)	2.41 (1.09-5.28)	3.32 (1.67-6.54)	4.43 (2.39-8.13)
Cardiovascular mortality	0.79 (0.11-5.50)	1.59 (0.40-6.22)	2.79 (0.89-8.61)	1.59 (0.60-4.18)	2.51 (1.13-5.51)	3.63 (1.81-7.18)
Rehospitalisation due to MI	0.80 (0.11-5.54)	2.49 (0.81-7.52)	3.88 (1.43-10.33)	4.02 (2.18-7.35)	5.39 (3.16-9.12)	8.38 (5.31-13.10)
Composite of cardiovascular death and rehospitalisation due to HF or MI	1.59 (0.40-6.20)	5.70 (2.76-11.60)	8.30 (4.32-15.61)	10.71 (7.47-15.23)	12.51 (8.96-17.32)	18.00 (13.40-23.94)
Composite of all-cause death, rehospitalisation due to MI or HF	2.38 (0.77-7.20)	7.26 (3.84-13.49)	11.34 (6.45-19.52)	11.50 (8.13-16.13)	13.28 (9.62-18.18)	18.72 (14.06-24.69)
Composite Endpoint of HF Incidence and Reinfarction (Rehospitalisation due to MI)	3.19 (1.21-8.27)	9.11 (5.15-15.86)	10.55 (6.06-18.06)	14.01 (10.26-18.97)	16.69 (12.56-21.99)	20.98 (16.13-27.05)
Composite Endpoint of Rehospitalization due to HF or MI	0.79 (0.11-5.50)	4.16 (1.75-9.72)	5.57 (2.48-12.26)	10.34 (7.16-14.82)	11.69 (8.27-16.40)	16.69 (12.25-22.2)
Composite Endpoint of Cardiovascular Mortality and Reinfarction (Rehospitalisation due to MI)	1.59 (0.40-6.20)	4.05 (1.70-9.46)	6.62 (3.14-13.66)	4.40 (2.46-7.82)	6.23 (3.80-10.14)	9.75 (6.41-14.68)
Composite Endpoint of All-Cause Mortality and Incidence of HF or MI (rehospitalization due to MI)	4.76 (2.17-10.29)	12.11 (7.48-19.28)	16.28 (10.39-25.02)	15.12 (11.24-20.19)	18.23 (13.93-23.65)	22.97 (17.94-29.14)
Composite Endpoint of Cardiovascular	3.97 (1.67-9.29)	10.60 (6.30-17.57)	13.24 (8.10-21.26)	14.36 (10.57-19.35)	17.49 (13.27-22.86)	22.27 (17.29-28.43)

Mortality and Incidence of HF or MI (rehospitalization due to MI)						

Supplementary Table D. Number of Events, Failure Rates, and Annual Incidence Rates of Endpoints in the PREVENT-TAHA8 Trial

Endpoints	Intervention (WJ-MSCs)			Control		
	Number of total events / person-year follow-up	Cumulative probability (estimates failure rates) at 3 years follow-up%: 95%CI	Annual incidence rate% (per 100 person-year): 95%CI	Number of total events / person-year follow-up	Cumulative probability (estimates failure rates) at 3 years follow-up%: 95%CI	Annual incidence rate% (per 100 person-year): 95%CI
HF incidence (development)	9 / 314.47	5.74: 1.99-9.50	2.77: 1.44-5.32	37 / 551.88	16.08: 10.90-21.27	6.48: 4.69-8.94
Rehospitalisation due to HF	3 / 325.39	2.48: 0.80-7.48	0.92: 0.30-2.86	24 / 570.98	10.77: 7.24-15.88	4.20: 2.82-6.27
All-cause mortality	6 / 331.24	5.85: 2.59-12.93	1.81: 0.81-4.03	10 / 602.66	4.43: 2.39-8.13	1.66: 0.89-3.08
Cardiovascular mortality	3 / 331.24	2.79: 0.89-8.61	0.91: 0.29-2.81	8 / 602.66	3.63%: 1.81%-7.18%	1.33: 0.66-2.65
Rehospitalisation due to MI	4 / 325.34	3.88: 1.43-10.33	1.23: 0.46-3.28	18 / 588.63	8.38: 5.31-13.10	3.06: 1.93-4.85
Composite of cardiovascular death and rehospitalisation due to HF or MI	9 / 321.81	8.30: 4.32-15.61	2.80: 1.45-5.37	40 / 558.59	18.00: 13.40-23.94	7.16: 5.25-9.76
Composite of all-cause death, rehospitalisation due to MI or HF	12 / 321.81	11.34: 6.45-19.52	3.72: 2.12-6.57	42 / 558.59	18.72: 14.06-24.69	7.52: 5.56-10.17
Composite Endpoint of HF Incidence and Reinfarction (Rehospitalisation due to MI)	12 / 310.89	10.55: 6.06-18.06	3.86: 2.19-6.80	48 / 539.85	20.98: 16.13-27.05	8.89: 6.70-11.80
Composite Endpoint of Rehospitalization due to HF or MI	6 / 321.81	5.57: 2.48-12.26	1.86: 0.84-4.15	37 / 558.36	16.69: 12.25-22.52	6.63: 4.80-9.15
Composite Endpoint of Cardiovascular Mortality and Reinfarction (Rehospitalisation due to MI)	7 / 325.34	6.62: 3.14-13.66	2.15: 1.03-4.51	21 / 588.60	9.75: 6.41-14.68	3.57: 2.33-5.47
Composite Endpoint of All-Cause Mortality	18 / 310.89	16.28: 10.39-25.02	5.79: 3.65-9.19	53 / 539.85	22.97: 17.94-29.14	9.82: 7.50-12.85

and Incidence of HF or MI (rehospitalization due to MI)						
Composite Endpoint of Cardiovascular Mortality and Incidence of HF or MI (rehospitalization due to MI)	15 / 310.89	13.24: 8.10-21.26	4.82: 2.91-8.00	51 / 539.85	22.27: 17.29-28.43	9.45: 7.18-12.43

Supplementary Table E. Crude and Adjusted Cox Regression Analysis of Primary and Secondary Outcomes

Outcome	Unadjusted Model	Model 1*	Model 2°	Model 3§	Model 4¤
HF Incidence (development)	0.43 (0.21-0.89)	0.44 (0.21-0.91)	0.44 (0.21-0.92)	0.58 (0.27-1.23)	0.49 (0.23-1.04)
P-value of treatment allocation in the model	0.024	0.028	0.029	0.158	0.117
P-value of model	0.014	0.009	0.020	0.326	0.407
P-value of global proportionality assumption test	0.103	0.323	0.200	0.451	0.407
Rehospitalisation due to HF	0.22 (0.07-0.75)	0.23 (0.07-0.78)	0.23 (0.07-0.78)	0.30 (0.09-1.03)	0.30 (0.09-1.04)
P-value of treatment allocation in the model	0.015	0.018	0.018	0.056	0.058
P-value of model	0.003	0.004	0.009	0.056	0.014
P-value of global proportionality assumption test	0.360	0.773	0.718	0.936	0.896
All-cause mortality	1.10 (0.40-3.02)	1.14 (0.42-3.16)	1.17 (0.42-3.22)	1.44 (0.45-4.61)	1.80 (0.55-5.93)
P-value of treatment allocation in the model	0.856	0.793	0.765	0.535	0.333
P-value of model	0.856	0.588	0.643	0.530	0.089
P-value of global proportionality assumption test	0.157	0.471	0.632	0.714	0.713
Cardiovascular Mortality	0.68 (0.18-2.56)	0.68 (0.18-2.56)	0.68 (0.18-2.57)	1.06 (0.25-4.49)	1.21 (0.28-5.28)
P-value of treatment allocation in the model	0.570	0.565	0.568	0.932	0.795
P-value of model	0.559	0.948	0.985	0.988	0.342
P-value of global proportionality assumption test	0.469	0.691	0.807	0.758	0.356
Rehospitalisation due to MI	0.40 (0.14-1.16)	0.39 (0.13-1.16)	0.39 (0.13-1.15)	0.57 (0.18-1.79)	0.61 (0.19-1.95)
P-value of treatment allocation in the model	0.099	0.090	0.087	0.338	0.409
P-value of model	0.0712	0.093	0.1613	0.822	0.783
P-value of global proportionality assumption test	0.286	0.323	0.293	0.475	0.662
Composite Endpoint of cardiovascular death and rehospitalization due to HF or MI	0.40 (0.19-0.81)	0.39 (0.19-0.81)	0.40 (0.19-0.82)	0.53 (0.25-1.13)	0.54 (0.25-1.16)
P-value of treatment allocation in the model	0.012	0.012	0.012	0.099	0.116
P-value of model	0.006	0.015	0.0328	0.197	0.202
P-value of global proportionality assumption test	0.075	0.175	0.227	0.0563	0.395
Composite Endpoint of all-cause death and	0.50 (0.26-0.96)	0.51 (0.27-0.96)	0.51 (0.27-0.98)	0.63 (0.31-1.25)	0.65 (0.32-1.32)

rehospitalisation due to HF or MI					
P-value of treatment allocation in the model	0.036	0.038	0.042	0.186	0.234
P-value of model	0.026	0.069	0.111	0.128	0.072
P-value of global proportionality assumption test	0.027	0.097	0.118	0.440	0.499
Composite Endpoint of HF Incidence (development) and Reinfarction (Rehospitalisation due to MI)	0.44 (0.23-0.82)	0.43 (0.23-0.82)	0.44 (0.23-0.83)	0.58 (0.30-1.12)	0.56 (0.29-1.09)
P-value of treatment allocation in the model	0.010	0.011	0.012	0.106	0.089
P-value of model	0.005	0.004	0.010	0.242	0.533
P-value of global proportionality assumption test	0.042	0.035	0.032	0.173	0.275
Composite Endpoint of rehospitalization due to HF or MI	0.29 (0.12-0.68)	0.29 (0.12-0.68)	0.29 (0.12-0.68)	0.38 (0.16-0.93)	0.39 (0.16-0.95)
P-value of treatment allocation in the model	0.005	0.005	0.005	0.034	0.039
P-value of model	0.001	0.002	0.005	0.076	0.070
P-value of global proportionality assumption test	0.106	0.294	0.314	0.668	0.682
Composite Endpoint of Cardiovascular Mortality and Reinfarction (Rehospitalisation due to MI)	0.60 (0.25-1.41)	0.58 (0.25-1.37)	0.58 (0.25-1.38)	0.86 (0.35-2.15)	0.93 (0.37-2.36)
P-value of treatment allocation in the model	0.243	0.215	0.219	0.749	0.885
P-value of model	0.2245	0.249	0.388	0.883	0.687
P-value of global proportionality assumption test	0.2673	0.234	0.293	0.464	0.458
Composite Endpoint of All-Cause Mortality and Incidence of HF or MI (rehospitalization due to MI)	0.59 (0.35-1.01)	0.60 (0.35-1.02)	0.60 (0.35-1.04)	0.75 (0.43-1.34)	0.74 (0.42-1.33)
P-value of treatment allocation in the model	0.056	0.058	0.067	0.335	0.317
P-value of model	0.047	0.052	0.067	0.274	0.536
P-value of global proportionality assumption test	0.008	0.009	0.009	0.100	0.179
Composite Endpoint of	0.51 (0.29-0.91)	0.51 (0.29-0.91)	0.52 (0.29-0.92)	0.69 (0.37-1.25)	0.67 (0.36-1.23)

Cardiovascular Mortality and Incidence of HF or MI (rehospitalization due to MI)					
P-value of treatment allocation in the model	0.023	0.023	0.026	0.220	0.195
P-value of model	0.016	0.019	0.034	0.399	0.745
P-value of global proportionality assumption test	0.028	0.017	0.021	0.133	0.133

*Adjusted for age and sex

°Adjusted for model 1 and baseline LVEF

§Adjusted for model 2, smoking, and obesity (BMI ≥30)

¤Adjusted for model 3 and comorbidities including anemia, diabetes, hypertension, hypercholesterolemia, and renal insufficiency (eGFR <60)

HF: heart failure, MI: myocardial infarction, LVEF: left ventricular ejection fraction, BMI: body mass index, and eGFR: estimated glomerular filtration rate using MDRD formula.

Scaled Schoenfeld residuals test P-values were obtained using the global test of proportionality assumption using "stphtest" Stata command.

Supplementary Table F. Optimized Cox Regression Models for Primary and Secondary Outcomes of PREVENT-TAHA8 Trial

Outcome	Covariates	Hazard ratio (95% CI)	P value	P-value of global proportionality assumption test
HF incidence	Intervention vs Control	0.44 (0.21-0.91)	0.028	0.259
	Female vs Male	2.19 (1.18-4.06)	0.013	
Rehospitalisation due to HF	Intervention vs Control	0.23 (0.07-0.78)	0.018	0.667
	Female vs Male	2.50 (1.14-5.46)	0.022	
Composite Endpoint of cardiovascular death and rehospitalization due to HF or MI	Intervention vs Control	0.40 (0.19-0.82)	0.012	0.075
Composite Endpoint of all-cause death and rehospitalization due to HF or MI	No acceptable finalized model.			
Composite Endpoint of HF Incidence and Reinfarction (Rehospitalisation due to MI)	Intervention vs Control	0.44 (0.23-0.83)	0.012	0.099
	Female vs Male	1.78 (1.01-3.12)	0.045	
Composite Endpoint of Rehospitalization due to HF or MI	Intervention vs Control	0.27 (0.12-0.68)	0.005	0.106
Composite Endpoint of Cardiovascular Mortality and Incidence of HF or MI (rehospitalization due to MI)	Intervention vs Control	0.51 (0.29-0.91)	0.023	0.028

Supplementary Table G. Evaluating Interactions in Cox Regression Models for Primary and Secondary Outcomes of PREVENT-TAHA8 Trial

Outcome	Patients group	Hazard ratio (95% CI)	P value	P-value of global proportionality assumption test
HF incidence	Male-Control	Ref	Ref	0.463
	Male-Intervention	0.60 (0.27-1.35)	0.217	
	Female-Intervention	0.38 (0.05-2.83)	0.346	
	Female-Control	2.68 (1.38-5.21)	0.004	
Rehospitalization due to HF	Male-Control	Ref	Ref	0.847
	Male-Intervention	0.23 (0.05-1.00)	0.051	
	Female-Intervention	0.61 (0.08-4.61)	0.631	
	Female-Control	2.48 (1.08-5.67)	0.031	
Composite Endpoint of HF Incidence and Reinfarction (Rehospitalisation due to MI)	Male-Control	Ref	Ref	0.231
	Male-Intervention	0.52 (0.26-1.05)	0.069	
	Female-Intervention	0.52 (0.12-2.15)	0.365	
	Female-Control	2.00 (1.08-3.68)	0.027	

Supplementary Table H. Subgroup Analysis of PREVENT-TAHA8 Outcomes

A. HF incidence

Subgroup	Intervention (WJ-MSC)		Control (standard care)		Hazard Ratio (95% CI)
	No. of patients with events/Total patients (%)		No. of patients with events/Total patients (%)		
Overall	9/136	6.62	37/260	14.23	0.43 (0.21-0.89)
Age					
<60	7/84	8.33	15/136	11.03	0.72 (0.29-1.76)
≥60	2/52	3.85	22/124	17.74	0.19 (0.04-0.82)
Gender					
Male	8/115	6.96	23/205	11.22	0.60 (0.27-1.35)
Female	1/21	4.76	14/55	25.45	0.15 (0.02-1.12)
Baseline LVEF					
≥30%	8/103	7.77	27/199	13.57	0.53 (0.24-1.18)
<30%	1/33	3.03	10/61	16.39	0.17 (0.02-1.34)
Smoking					
No	3/51	5.88	15/85	17.65	0.30 (0.09-1.05)
Yes	6/73	8.22	14/136	10.29	0.76 (0.29-1.98)
Obesity (BMI ≥ 30)					
No	7/89	7.87	19/157	12.10	0.62 (0.26-1.47)
Yes	2/28	7.14	8/51	15.69	0.46 (0.10-2.16)
Anemia					
No	8/113	7.08	34/208	16.35	0.39 (0.18-0.85)
Yes	1/23	4.35	3/52	5.77	0.76 (0.08-7.30)
Hypertension					
No	4/79	5.06	19/143	13.29	0.36 (0.12-1.06)
Yes	5/57	8.77	18/117	15.38	0.51 (0.19-1.39)
Diabetes					
No	6/99	6.06	22/192	11.46	0.50 (0.20-1.24)
Yes	3/25	12.00	8/30	26.67	0.39 (0.10-1.49)
Hypercholesterolemia					
No	6/94	6.38	26/175	14.86	0.39 (0.16-0.97)
Yes	3/42	7.14	11/85	12.94	0.49 (0.14-1.79)
Renal Insufficiency (eGFR < 60)					
No	9/118	7.63	29/221	13.12	0.55 (0.26-1.16)
Yes	0/18	0.00	8/39	20.51	—
At least one of five mentioned comorbidities					
No	3/45	6.67	12/77	15.58	0.40 (0.11-1.41)
Yes	6/91	6.59	25/183	13.66	0.45 (0.18-1.09)

B. Rehospitalisation due to HF

Subgroup	Intervention (WJ-MSC)		Control (standard care)		Hazard Ratio (95% CI)
	No. of patients with events/Total patients (%)		No. of patients with events/Total patients (%)		
Overall	3/136	2.21	24/260	9.23	0.22 (0.07-0.75)
Age					
<60	3/84	3.57	10/136	7.35	0.46 (0.13-1.68)
≥60	0/52	0.00	14/124	11.29	-
Gender					
Male	2/115	1.74	15/205	7.32	0.23 (0.05-0.99)
Female	1/21	4.76	9/55	16.36	0.25 (0.03-1.97)
Baseline LVEF					
≥30%	2/103	1.94	18/199	9.05	0.20 (0.05-0.87)
<30%	1/33	3.03	6/61	9.84	0.29 (0.03-2.41)
Smoking					
No	1/51	1.96	7/85	8.24	0.23 (0.03-1.87)
Yes	2/73	2.74	11/136	8.09	0.32 (0.07-1.46)
Obesity (BMI ≥ 30)					
No	3/89	3.37	10/157	6.37	0.51 (0.14-1.86)
Yes	0/28	0.00	8/51	15.69	-
Anemia					
No	2/113	1.77	23/208	11.06	0.15 (0.03-0.63)
Yes	1/23	4.35	1/52	1.92	2.37 (0.15-37.83)
Hypertension					
No	0/79	0.00	11/143	7.69	-
Yes	3/57	5.26	13/117	11.11	0.43 (0.12-1.54)
Diabetes					
No	2/99	2.02	15/192	7.81	0.25 (0.06-1.09)
Yes	1/25	4.00	4/30	13.33	0.28 (0.03-2.50)
Hypercholesterolemia					
No	2/94	2.13	18/175	10.29	0.19 (0.04-0.83)
Yes	1/42	2.38	6/85	7.06	0.32 (0.04-2.64)
Renal Insufficiency (eGFR < 60)					
No	3/118	2.54	20/221	9.05	0.27 (0.08-0.90)
Yes	0/18	0.00	4/39	10.26	-
At least one of five mentioned comorbidities					
No	0/45	0.00	9/77	11.69	-
Yes	3/91	3.30	15/183	8.20	0.39 (0.11-1.34)

C. Composite endpoint of cardiovascular mortality and rehospitalization due to HF or MI

Subgroup	Intervention (WJ-MSC)		Control (standard care)		Hazard Ratio (95% CI)
	No. of patients with events/Total patients (%)		No. of patients with events/Total patients (%)		
Overall	9/136	6.62	40/260	15.38	0.40 (0.19-0.82)
Age					
<60	8/84	9.52	21/136	15.44	0.57 (0.25-1.27)
≥60	1/52	1.92	19/124	15.32	0.11 (0.01-0.85)
Gender					
Male	7/115	6.09	30/205	14.63	0.40 (0.17-0.90)
Female	2/21	9.52	10/55	18.18	0.44 (0.09-2.00)
Baseline LVEF					
≥30%	7/103	6.80	29/199	14.57	0.43 (0.19-0.98)
<30%	2/33	6.06	11/61	18.03	0.31 (0.07-1.40)
Smoking					
No	3/51	5.88	10/85	11.76	0.48 (0.13-1.76)
Yes	6/73	8.22	21/136	15.44	0.50 (0.20-1.24)
Obesity (BMI ≥ 30)					
No	8/89	8.99	18/157	11.46	0.75 (0.33-1.73)
Yes	1/28	3.57	11/51	21.57	0.16 (0.02-1.23)
Anemia					
No	7/113	6.19	32/208	15.38	0.37 (0.16-0.83)
Yes	2/23	8.70	8/52	15.38	0.54 (0.12-2.57)
Hypertension					
No	3/79	3.80	22/143	15.38	0.23 (0.07-0.76)
Yes	6/57	10.53	18/117	15.38	0.63 (0.25-1.58)
Diabetes					
No	7/99	7.07	27/192	14.06	0.48 (0.21-1.10)
Yes	2/25	8.00	5/30	16.67	0.44 (0.09-2.29)
Hypercholesterolemia					
No	7/94	7.45	29/175	16.57	0.41 (0.18-0.95)
Yes	2/42	4.76	11/85	12.94	0.34 (0.07-1.52)
Renal Insufficiency (eGFR < 60)					
No	8/118	6.78	35/221	15.84	0.40 (0.18-0.86)
Yes	1/18	5.56	5/39	12.82	0.40 (0.05-3.45)
At least one of five mentioned comorbidities					
No	2/45	4.44	13/77	16.88	0.24 (0.05-1.06)
Yes	7/91	7.69	27/183	14.75	0.48 (0.21-1.11)

D. Composite endpoint of all-cause mortality and rehospitalization due to HF or MI

Subgroup	Intervention (WJ-MSC)		Control (standard care)		Hazard Ratio (95% CI)
	No. of patients with events/Total patients (%)		No. of patients with events/Total patients (%)		
Overall	12/136	8.82	42/260	16.15	0.50(0.26-0.96)
Age					
<60	8/84	9.52	21/136	15.44	0.57 (0.25-1.28)
≥60	4/52	7.69	21/124	16.94	0.41 (0.14-1.20)
Gender					
Male	9/115	7.83	31/205	15.12	0.49 (0.23-1.04)
Female	3/21	14.29	11/55	20.00	0.60 (0.17-2.17)
Baseline LVEF					
≥30%	10/103	9.71	31/199	15.58	0.57 (0.28-1.17)
<30%	2/33	6.06	11/61	18.03	0.31 (0.07-1.40)
Smoking					
No	4/47	8.51	11/85	12.94	0.58 (0.19-1.83)
Yes	8/73	10.96	22/136	16.18	0.64 (0.29-1.44)
Obesity (BMI ≥ 30)					
No	9/89	10.11	19/157	12.10	0.80 (0.36-1.77)
Yes	2/28	7.14	12/51	23.53	0.29 (0.06-1.28)
Anemia					
No	10/113	8.85	33/208	15.87	0.51(0.25-1.04)
Yes	2/23	8.70	9/52	17.31	0.49 (0.10-2.26)
Hypertension					
No	4/79	5.06	23/143	16.08	0.29 (0.10-0.84)
Yes	8/57	14.04	19/117	16.24	0.79 (0.35-1.81)
Diabetes					
No	10/99	10.10	29/192	15.10	0.64 (0.31-1.31)
Yes	2/25	8.00	5/30	16.67	0.44 (0.09-2.29)
Hypercholesterolemia					
No	10/94	10.64	31/175	17.71	0.55 (0.27-1.13)
Yes	2/42	4.76	11/85	12.94	0.34 (0.07-1.52)
Renal Insufficiency (eGFR < 60)					
No	10/118	8.47	37/221	16.74	0.47 (0.23-0.94)
Yes	2/18	11.11	5/39	12.82	0.81 (0.16-4.20)
At least one of five mentioned comorbidities					
No	3/45	6.67	14/77	18.18	0.33 (0.10-1.16)
Yes	9/91	9.89	28/183	15.30	0.60 (0.28-1.28)

E. HF incidence or rehospitalization due to MI

Subgroup	Intervention (WJ-MSC)		Control (standard care)		Hazard Ratio (95% CI)
	No. of patients with events/Total patients (%)		No. of patients with events/Total patients (%)		
Overall	12/136	8.82	48/260	18.46	0.44 (0.23-0.82)
Age					
<60	10/84	11.90	24/136	17.65	0.63 (0.30-1.31)
≥60	2/52	3.85	24/124	19.35	0.18 (0.04-0.74)
Gender					
Male	10/115	8.70	33/205	16.10	0.52 (0.26-1.05)
Female	2/21	9.52	15/55	27.27	0.27 (0.06-1.18)
Baseline LVEF					
≥30%	10/103	9.71	34/199	17.09	0.52 (0.26-1.06)
<30%	2/33	6.06	14/61	22.95	0.24 (0.05-1.05)
Smoking					
No	4/51	7.84	38/226	20.00	0.36 (0.12-1.06)
Yes	8/73	10.96	21/136	15.44	0.68 (0.30-1.53)
Obesity (BMI ≥ 30)					
No	9/89	10.11	25/157	15.92	0.60 (0.28-1.28)
Yes	3/28	10.71	10/51	19.61	0.54 (0.15-1.96)
Anemia					
No	11/113	9.73	40/208	19.23	0.46 (0.24-0.89)
Yes	1/23	4.35	8/52	15.38	0.27 (0.03-2.14)
Hypertension					
No	5/79	6.33	28/143	19.58	0.30 (0.11-0.77)
Yes	7/57	12.28	20/117	17.09	0.65 (0.27-1.54)
Diabetes					
No	8/99	8.08	31/192	16.15	0.47 (0.22-1.03)
Yes	4/25	16.00	8/30	26.67	0.53 (0.16-1.76)
Hypercholesterolemia					
No	9/94	9.57	34/174	19.43	0.45 (0.22-0.95)
Yes	3/42	7.14	14/85	16.47	0.39 (0.11-1.34)
Renal Insufficiency (eGFR < 60)					
No	12/118	10.17	39/221	17.65	0.54 (0.28-1.03)
Yes	0/18	0.00	9/39	23.08	-
At least one of five mentioned comorbidities					
No	4/45	8.89	15/77	19.48	0.42 (0.14-1.27)
Yes	8/91	8.79	33/183	18.03	0.45 (0.21-0.96)

F. Rehospitalization due to HF or MI

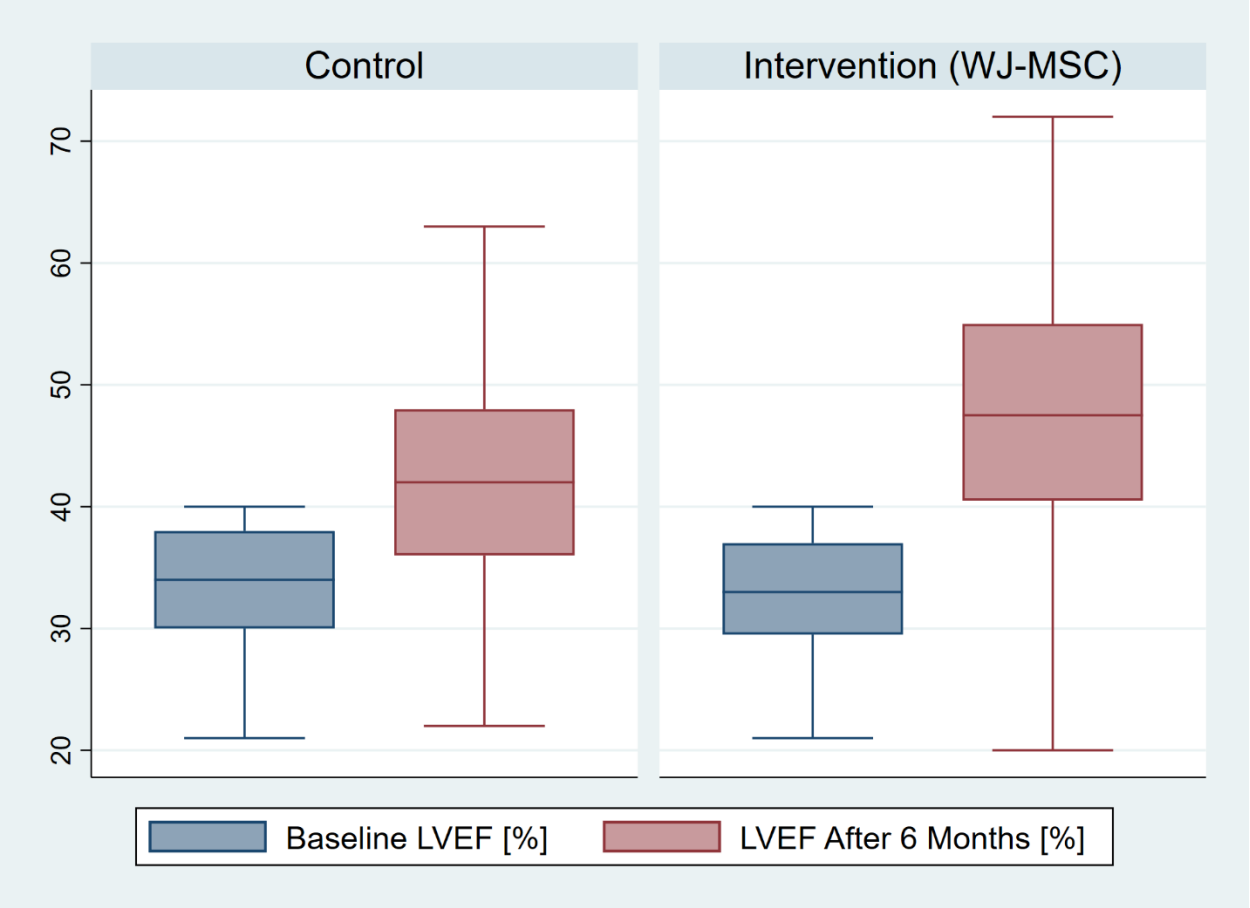
Subgroup	Intervention (WJ-MSC)		Control (standard care)		Hazard Ratio (95% CI)
	No. of patients with events/Total patients (%)		No. of patients with events/Total patients (%)		
Overall	6/136	4.41	37/260	14.23	0.29 (0.12-0.68)
Age					
<60	6/84	7.14	21/136	14.71	0.45 (0.18-1.12)
≥60	0/52	0.00	17/124	13.71	-
Gender					
Male	4/115	3.48	27/205	13.17	0.25 (0.09-0.72)
Female	2/21	9.52	10/55	18.18	0.44 (0.09-2.00)
Baseline LVEF					
≥30%	4/103	3.88	26/199	13.07	0.27 (0.10-0.78)
<30%	2/33	6.06	11/61	18.03	0.31 (0.07-1.40)
Smoking					
No	2/51	3.92	10/85	11.76	0.32 (0.07-1.47)
Yes	4/73	5.48	18/136	13.24	0.39 (0.13-1.16)
Obesity (BMI ≥ 30)					
No	5/89	5.62	17/157	10.83	0.50 (0.18-1.35)
Yes	1/28	3.57	10/51	19.61	0.17 (0.02-1.36)
Anemia					
No	5/113	4.42	30/208	14.42	0.28 (0.11-0.72)
Yes	1/23	4.35	7/52	13.46	0.31 (0.04-2.51)
Hypertension					
No	1/79	1.27	21/143	14.69	0.08 (0.01-0.59)
Yes	5/57	8.77	16/117	13.68	0.59 (0.22-1.61)
Diabetes					
No	4/99	4.04	24/192	12.50	0.31 (0.11-0.89)
Yes	2/25	8.00	5/30	16.67	0.44 (0.09-2.29)
Hypercholesterolemia					
No	5/94	5.32	27/175	15.43	0.32 (0.12-0.83)
Yes	1/42	2.38	10/85	11.76	0.19 (0.02-1.45)
Renal Insufficiency (eGFR < 60)					
No	6/118	5.08	32/221	14.48	0.33 (0.14-0.78)
Yes	0/18	0.00	5/39	12.82	-
At least one of five mentioned comorbidities					
No	1/45	2.22	13/77	16.88	0.12 (0.02-0.92)
Yes	5/91	5.49	24/183	13.11	0.39 (0.15-1.03)

G. Composite endpoint of cardiovascular mortality and HF or MI incidence

Subgroup	Intervention (WJ-MSC)		Control (standard care)		Hazard Ratio (95% CI)
	No. of patients with events/Total patients (%)		No. of patients with events/Total patients (%)		
Overall	15/136	11.03	51/260	19.62	0.51 (0.29-0.91)
Age					
<60	12/84	14.29	25/136	18.38	0.72 (0.36-1.43)
≥60	3/52	5.77	26/124	20.97	0.24 (0.07-0.80)
Gender					
Male	13/115	11.30	36/205	17.56	0.62 (0.33-1.17)
Female	2/21	9.52	15/55	27.27	0.27 (0.06-1.18)
Baseline LVEF					
≥30%	13/103	12.62	37/199	18.59	0.62 (0.33-1.18)
<30%	2/33	6.06	14/61	22.95	0.24 (0.05-1.05)
Smoking					
No	5/51	9.80	38/226	20.00	0.45 (0.16-1.21)
Yes	10/73	13.70	24/136	17.65	0.74 (0.35-1.55)
Obesity (BMI ≥ 30)					
No	12/89	13.48	26/157	16.56	0.77 (0.39-1.52)
Yes	3/28	10.71	11/51	21.57	0.49 (0.14-1.77)
Anemia					
No	13/113	11.50	42/208	20.19	0.52 (0.28-0.96)
Yes	2/23	8.70	9/52	17.31	0.48 (0.10-2.21)
Hypertension					
No	7/79	8.86	29/143	20.28	0.40 (0.18-0.92)
Yes	8/57	14.04	22/117	18.80	0.67 (0.30-1.51)
Diabetes					
No	11/99	11.11	34/192	17.71	0.59 (0.30-1.17)
Yes	4/25	16.00	8/30	26.67	0.53 (0.16-1.76)
Hypercholesterolemia					
No	11/94	11.70	36/174	20.57	0.52 (0.27-1.03)
Yes	4/42	9.52	15/85	17.65	0.48 (0.16-1.45)
Renal Insufficiency (eGFR < 60)					
No	14/118	11.86	42/221	19.00	0.58 (0.32-1.07)
Yes	1/18	5.56	9/39	23.08	0.21 (0.03-1.64)
At least one of five mentioned comorbidities					
No	5/45	11.11	15/77	19.48	0.53 (0.19-1.45)
Yes	10/91	10.99	36/183	19.67	0.51 (0.25-1.03)

LVEF change at 6-month follow-up analysis

A. Box Plot of Baseline and 6-Months LVEF



B. Wilcoxon Test Results

	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 (WJ-MSC)	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 the groups				0.000

*Wilcoxon matched-pairs signed-rank test were used to assess differences between post-six-month LVEF and baseline LVEF within both the intervention and control groups. To compare LVEF changes between treatment groups, the Wilcoxon rank-sum test was conducted.

C. T Test Results

	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 (WJ-MSC)	32.97 (4.86)	47.14 (9.56)	14.28 (8.63)	0.000
P-value of two independent sample t test for comparison of LVEF change between the groups				0.000

*Paired t test were used to assess differences between post-six-month LVEF and baseline LVEF within both the intervention and control groups. To compare LVEF changes between treatment groups, the two independent sample t test was conducted.

D. Linear regression analysis of LVEF change within 6 months post AMI

	Unadjusted Model	Model 1*	Model 2°	Model 3§	Model 4¤
Coefficient (Intervention vs Control)	6.11 (4.39-7.84)	6.06 (4.33-7.79)	5.97 (4.25-7.70)	5.85 (3.98-7.72)	5.88 (4.00-7.76)
P-value	0.000	0.000	0.000	0.000	0.000

*Adjusted for age and sex

°Adjusted for model 1 and baseline LVEF

§Adjusted for model 2, smoking, and obesity (BMI ≥30)

¤Adjusted for model 3 and comorbidities including anemia, diabetes, hypertension, hypercholesterolemia, and renal insufficiency (eGFR <60)