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Targeting Mitochondrial Bioenergetics with a Triple-Component Supplement Accelerates Post-Infarction Myocardial Recovery:

A Randomized, Double-Blind, Placebo-Controlled Trial

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Targeting Mitochondrial Bioenergetics with a Triple-Component Supplement Accelerates Post-Infarction Myocardial Recovery: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Myocardial infarction (MI) leads to persistent mitochondrial dysfunction, impaired ATP production, and oxidative stress, delaying cardiac recovery even after successful reperfusion. We evaluated the efficacy and safety of a mitochondrial-targeted combination therapy (Cardiotrition® Booster: Coenzyme Q10, acetyl L-carnitine, and alpha-lipoic acid) in post-MI patients.

Methods: In this multicenter, randomized, double-blind, placebo-controlled trial, 184 patients aged 35–75 years within 14 days of MI or percutaneous coronary intervention were randomized 1:1 to receive either the intervention or placebo for 30 days, followed by a 15-day safety follow-up. The primary endpoint was percentage improvement in the Myocardial Functional Recovery Index (MFRI), a composite of left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), and NT-proBNP reduction. Secondary endpoints included LVEF, NT-proBNP, oxidative stress biomarkers (malondialdehyde [MDA], glutathione [GSH], total antioxidant capacity [TAC]), NYHA class, 6-minute walk distance (6MWT), and time-to-recovery.

Results: The intervention group showed significantly greater MFRI improvement than placebo (48.2% ± 12.4 vs. 22.7% ± 10.1; *p* < 0.001; Cohen's *d* = 2.27). LVEF increased by +9.8% vs. +3.2% (*p* < 0.001); NT-proBNP decreased by −28% vs. −8.3% (*p* < 0.01); MDA decreased by −32% vs. −9%, GSH increased by +38% vs. +11%, and TAC increased by +41% vs. +13% (all *p* < 0.001). Functional outcomes improved: ≥1 NYHA class improvement in 63% vs. 28%; 6MWT distance increased by +90 m vs. +34 m (*p* < 0.001). Median recovery time was reduced from 32 to 16 days. No serious adverse events occurred.

Conclusions: Mitochondrial-targeted combination therapy with Cardiotrition® Booster significantly enhances myocardial recovery, improves cardiac function, and reduces oxidative stress in post-MI patients, representing a promising adjunctive strategy for cardiac rehabilitation.

KEYWORDS

Myocardial infarction; mitochondrial dysfunction; Coenzyme Q10; L-carnitine; alpha-lipoic acid; oxidative stress; cardiac rehabilitation; randomized controlled trial; NT-proBNP; left ventricular function

INTRODUCTION

Acute myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide despite substantial advances in early reperfusion strategies, including percutaneous coronary intervention (PCI) and thrombolytic therapy. While these interventions effectively restore epicardial coronary blood flow, a considerable proportion of patients continue to experience suboptimal myocardial recovery, characterized by persistent contractile dysfunction, adverse ventricular remodeling, and progression toward heart failure. This discrepancy highlights a critical limitation of current therapeutic paradigms, which primarily address macrovascular obstruction but inadequately target the underlying cellular and subcellular mechanisms of myocardial injury and repair.

Acute myocardial infarction (MI) remains a leading cause of morbidity and mortality worldwide despite substantial advances in early reperfusion strategies, including percutaneous coronary intervention (PCI) and thrombolytic therapy (Ibanez et al., 2018; O'Gara et al., 2013). While these interventions effectively restore epicardial coronary blood flow, a considerable proportion of patients continue to experience suboptimal myocardial recovery, characterized by persistent contractile dysfunction, adverse ventricular remodeling, and progression toward heart failure (Turer & Hill, 2010). This discrepancy highlights a critical limitation of current therapeutic paradigms, which primarily address macrovascular obstruction but inadequately target the underlying cellular and subcellular mechanisms of myocardial injury and repair.

At the core of post-MI pathophysiology lies profound mitochondrial dysfunction. Cardiomyocytes are highly energy-dependent cells, with mitochondria responsible for generating more than 90% of intracellular adenosine triphosphate (ATP) through oxidative phosphorylation (Brown et al., 2017). Ischemia-reperfusion injury induces structural and functional damage to mitochondrial membranes, impairs electron transport chain activity, and disrupts ATP synthesis (Zhou & Tian, 2018). Concurrently, excessive production of reactive oxygen species (ROS) overwhelms endogenous antioxidant defenses, resulting in oxidative damage to lipids, proteins, and mitochondrial DNA (Murphy, 2009). This cascade contributes to impaired calcium handling, activation of apoptotic pathways, and progressive deterioration of myocardial contractility (Madamanchi & Runge, 2007).

Oxidative stress plays a central role in mediating post-infarction myocardial injury and remodeling. Elevated levels of lipid peroxidation markers, such as malondialdehyde (MDA), alongside depletion of key antioxidants including reduced glutathione (GSH) and total antioxidant capacity (TAC), have been consistently associated with worse clinical outcomes (Ridker, 2003; Pfeffer et al., 2019). Moreover, neurohormonal activation and increased wall stress, reflected by elevated natriuretic peptides such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), further exacerbate myocardial dysfunction and delay functional recovery (Rossello & Yellon, 2020).

Given this pathophysiological framework, therapeutic strategies targeting mitochondrial bioenergetics and oxidative stress have emerged as promising adjuncts in post-MI management (Hausenloy et al., 2017; Andreadou et al., 2020). Among these, Coenzyme Q10 (CoQ10), L-carnitine, and alpha-lipoic acid (ALA) have been extensively investigated for their cardiometabolic and cytoprotective properties. CoQ10, a key component of the mitochondrial electron transport chain, facilitates electron transfer between complexes I/II and III, thereby enhancing ATP production and reducing electron leakage that generates ROS (Mortensen et al., 2014). Clinical studies have demonstrated that CoQ10 supplementation improves endothelial function, reduces oxidative stress, and may enhance left ventricular function in patients with cardiovascular disease (Lee et al., 2012).

L-carnitine plays a critical role in mitochondrial fatty acid metabolism by facilitating the transport of long-chain fatty acids into the mitochondrial matrix for β-oxidation (DiNicolantonio et al., 2013). This process is essential for maintaining energy production in the myocardium, particularly under conditions of metabolic stress. In the context of ischemia-reperfusion injury, L-carnitine has been shown to reduce infarct size, improve metabolic efficiency, and attenuate apoptosis (Lopaschuk et al., 2021). Alpha-lipoic acid is a potent antioxidant with both lipid- and water-soluble properties, enabling it to act across multiple cellular compartments (Shay et al., 2009). It not only directly scavenges reactive oxygen species but also regenerates endogenous antioxidants, including glutathione, vitamin C, and vitamin E (Sies, 2015).

Although each of these agents has demonstrated individual therapeutic benefits, the concept of combination mitochondrial-targeted therapy remains underexplored in clinical settings (Wang et al., 2021). Given their complementary mechanisms of action—enhancing ATP production (CoQ10), optimizing substrate utilization (L-carnitine), and restoring redox balance (ALA)—their combined use may produce synergistic effects that surpass those of single-agent interventions (Sverdlov et al., 2022). This integrated approach has the potential to simultaneously address multiple pathological axes of post-MI recovery, including energy deficiency, oxidative damage, and impaired functional capacity.

Despite the strong mechanistic rationale, there remains a significant clinical gap in the development and validation of therapies specifically designed to accelerate myocardial recovery following MI (Ong et al., 2021). Current standard-of-care treatments, including antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors, and statins, primarily target hemodynamic and neurohormonal pathways but do not directly restore mitochondrial function (Ardehali et al., 2020). Consequently, patients often experience prolonged recovery periods, reduced exercise tolerance, and increased risk of long-term complications (Bøtker et al., 2022).

To address this unmet need, the present study investigates the efficacy of Cardiotrition® Booster, a mitochondrial-targeted combination therapy comprising CoQ10, acetyl L-carnitine, and alpha-lipoic acid, in enhancing myocardial recovery in post-MI patients. This study introduces a novel composite endpoint—the Myocardial Functional Recovery Index (MFRI)—which integrates structural, functional, and biochemical parameters to provide a comprehensive assessment of cardiac recovery. **Abstract** provides a visual summary of the study rationale and main findings.

We hypothesized that administration of Cardiotrition® Booster during the early post-infarction period would (i) significantly improve myocardial functional recovery, (ii) enhance left ventricular performance, (iii) reduce oxidative stress and neurohormonal activation, and (iv) accelerate overall rehabilitation compared with placebo.

METHODS

2.1 Study Design and Oversight

This study was designed as a prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial conducted across three tertiary-care cardiology and cardiac rehabilitation centers. The trial duration consisted of a 30-day treatment phase, followed by a 15-day post-treatment safety follow-up, yielding a total study duration of 45 days. The study protocol was developed in accordance with the principles outlined in the Declaration of Helsinki and

2.2 Study Population

2.2.1 Recruitment and Setting

A total of 184 patients were recruited between December, 2024 and March, 2025 from cardiology departments and post-PCI rehabilitation units. Eligible patients were screened within 14 days of acute MI or coronary revascularization.

2.2.2 Inclusion Criteria

Participants were eligible if they met all of the following criteria: age between 35 and 75 years; confirmed diagnosis of acute MI (STEMI or NSTEMI) treated with PCI or thrombolysis within the preceding 14 days; left ventricular ejection fraction (LVEF) between 35% and 55% at baseline; hemodynamically stable at the time of enrollment; ability to provide informed consent and comply with study procedures.

2.2.3 Exclusion Criteria

Patients were excluded if they met any of the following: severe arrhythmias (e.g., sustained ventricular tachycardia, ventricular fibrillation, uncontrolled atrial fibrillation); significant renal impairment (eGFR < 45 mL/min/1.73 m²); hepatic dysfunction (AST/ALT >3× upper limit of normal); active infection or systemic inflammatory disease; current use of antioxidant or mitochondrial-targeted supplements within 30 days; pregnancy or lactation; participation in another clinical trial within the past 30 days.

adhered to Good Clinical Practice (GCP) guidelines. Ethical approval was obtained from the institutional review boards (IRBs) of all participating centers prior to study initiation. All participants provided written informed consent before enrollment. An independent data monitoring committee (DMC) oversaw study conduct, safety reporting, and interim data integrity. The trial followed CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized controlled trials.

2.3 Randomization and Blinding

Participants were randomized in a 1:1 ratio to receive either Cardiotrition® Booster or placebo using a computer-generated block randomization scheme (block size = 4), stratified by: age group (<60 vs. ≥60 years), baseline LVEF (<45% vs. ≥45%), and type of MI intervention (PCI vs. thrombolysis). Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes prepared by an independent statistician. This trial employed a triple-blind design, whereby participants, investigators and clinical staff, and outcome assessors and statisticians were all blinded to treatment allocation. Blinding integrity was assessed at study completion using Bang's Blinding Index, confirming adequate masking.

FIGURE 1: Double Blind, Randomized 1:1 Allocation Design

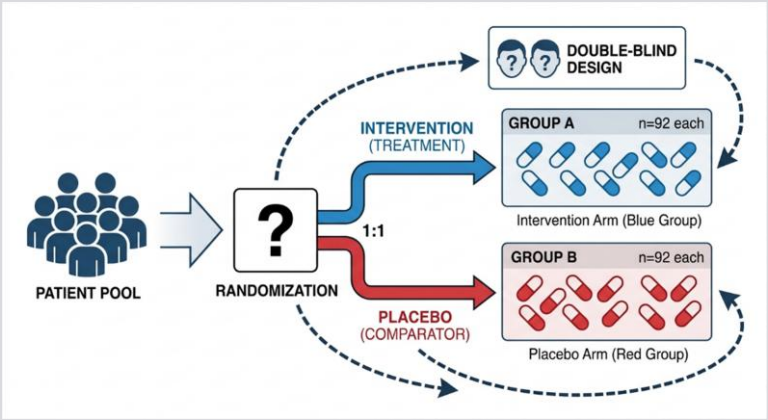

Figure 1. Schematic representation of the randomization and blinding scheme. A total of 184 patients were allocated in a 1:1 ratio to either the intervention arm (Cardiotrition® Booster, blue) or the placebo arm (red). The double-blind design ensured that participants, investigators, and outcome assessors were masked to treatment allocation.

2.4 Intervention and Study Treatment

2.4.1 Investigational Product

The investigational product, Cardiotrition® Booster, is a mitochondrial-targeted combination therapy formulated to enhance myocardial bioenergetics, reduce oxidative stress, and improve cardiac functional recovery following acute MI. The formulation integrates Coenzyme Q10 (CoQ10), alpha-lipoic acid (ALA), and acetyl L-carnitine (ALCAR) within advanced delivery systems designed to optimize bioavailability, cellular uptake, and cardiac tissue targeting.

2.4.2 Dosing Regimen

Participants assigned to the intervention group received Cardiotrition® Booster with the following structured dosing protocol: **Loading Phase (Day 0–7):** 2 tablets per day, administered after meals (one after breakfast and one after dinner); **Maintenance Phase (Day 8–30):** 1 tablet per day, administered after breakfast. This biphasic dosing strategy was designed to achieve rapid mitochondrial saturation during the early post-infarction phase, followed by sustained support throughout the recovery period.

2.4.3 Composition (Per Tablet)

Table 2.4.3: Composition of Cardiotrition® Booster (per tablet)

Component	Dose	Functional Role
INNOVA® Coenzyme Q10 (Liposomal CoQ10)	200 mg	Electron transport chain support, ATP production, antioxidant
INNOVA® Alpha-Lipoic Acid (Liposomal R-ALA)	300 mg	Redox modulation, antioxidant regeneration, mitochondrial enzyme activation
Acetyl L-Carnitine (ALCAR)	500 mg	Fatty acid transport, β-oxidation, mitochondrial energy metabolism

2.4.4 Advanced Delivery Technologies

To overcome known limitations of conventional oral supplementation—poor bioavailability, rapid degradation, and limited tissue targeting—the formulation incorporates two complementary delivery platforms: **CardioDrone® Technology** (targeted cardiac delivery using dual-ligand peptides) and **INNOVA3® Liposomal Delivery System** (multi-layered liposomes enhancing stability, absorption, and sustained intracellular activity). The placebo consisted of inert microcrystalline cellulose tablets identical in appearance, color, taste, packaging, and administration schedule.

2.4.5 Treatment Adherence

Adherence was assessed using tablet count at each visit, weekly follow-up calls, and

patient-reported compliance diaries. Participants demonstrating <80% adherence were included in the ITT analysis but excluded from per-protocol sensitivity analyses. The placebo consisted of inert microcrystalline cellulose tablets identical in: appearance, color, taste, packaging, and administration schedule to maintain full blinding integrity.

2.5 Outcome Measures

2.5.1 Primary Endpoint

The primary endpoint was the percentage change in the Myocardial Functional Recovery Index (MFRI) from baseline to Day 30. MFRI is a composite index integrating LVEF, global longitudinal strain (GLS), and NT-proBNP reduction, calculated as:

$$MFRI = \frac{1}{3}\left[\left(\frac{\Delta \text{LVEF}}{Baseline\ \text{LVEF}}\right) \times 100 + \left(\frac{\Delta \text{GLS}}{Baseline\ \text{GLS}}\right) \times 100 + \left(\frac{\Delta \text{NT} - \text{proBNP}}{Baseline\ \text{NT} - \text{proBNP}}\right) \times (-100)\right]$$

Where:

- $\Delta LVEF = LVEF_{30d} - LVEF_{baseline}$
- $\Delta GLS = GLS_{30d} - GLS_{baseline}$
- NT-proBNP reduction is multiplied by **(–100)** to reflect improvement direction

Higher MFRI values indicate superior myocardial recovery; values ≥ 30% were predefined as clinically meaningful.

2.5.2 Secondary Endpoints

Secondary outcomes included: change in LVEF and GLS; biochemical markers (NT-proBNP, hs-cTnT, CK-MB, hs-CRP); oxidative stress biomarkers (MDA, GSH, TAC); functional outcomes (NYHA class improvement, 6-minute walk test [6MWT], Return-to-Activity Index); and recovery kinetics (time-to-recovery by Kaplan-Meier analysis).

2.6 Clinical and Laboratory Assessments

Table 1. Study Assessment Timeline

Visit	Day	Assessments
V0	Day 0	Baseline labs, ECG, Echo, FSS, QoL
V1	Day 7	Biomarkers, vitals
V2	Day 15	Echo, NYHA, biomarkers
V3	Day 30	Full labs, Echo, ECG, 6MWT
V4	Day 45	Safety follow-up

Echocardiography was performed using standardized protocols (Simpson's biplane method for LVEF, speckle-tracking for GLS) according to ASE/EACVI guidelines, interpreted by blinded cardiologists. Biomarker analysis used validated assays: MDA by TBARS, GSH by Ellman method, TAC by FRAP, NT-proBNP by electrochemiluminescence, hs-troponin T by ECL, and hs-CRP by immunoturbidimetry. Functional assessments included 6MWT (per ATS guidelines), NYHA classification, Fatigue Severity Scale (FSS), and EQ-5D-5L for quality of life.

Table 1 below summarizes the assessment schedule. The timeline is also visualized in **Figure 2**.

FIGURE 2: Study Design and Participant Timeline

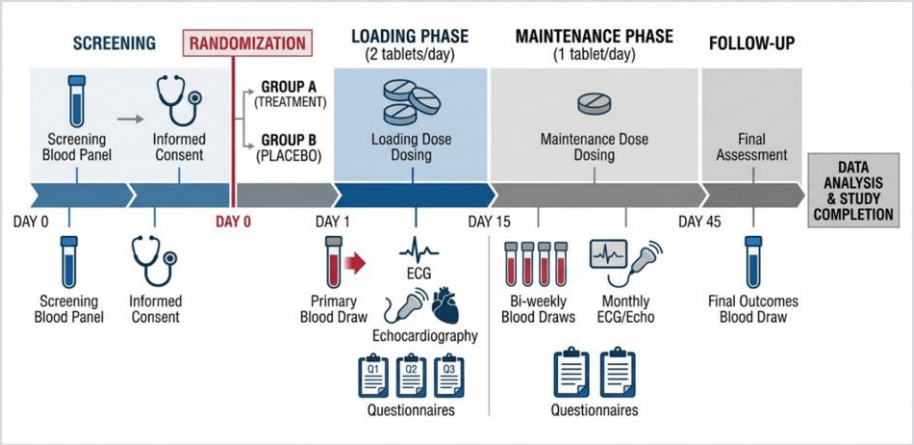

Figure 2. Flow diagram of the trial design and assessment schedule. Following screening and informed consent, 184 patients were randomized 1:1 to receive either Cardiotrition® Booster or placebo. The protocol comprised a 7-day loading phase (2 tablets/day) followed by a 23-day maintenance phase (1 tablet/day), with a 15-day post treatment safety follow up. Assessments included blood panels, ECG, echocardiography, and questionnaires at baseline (Day 0), Day 1, Day 15, and Day 45.

2.7 Sample Size Calculation

Sample size was calculated to detect a minimum clinically significant difference of 20% in MFRI between groups with power (1-β) = 80%, significance level $\alpha = 0.05$, assuming a standard deviation of 12%. A minimum of 82 patients per group was required. Accounting for an estimated 10% dropout rate, the final sample size was set at 184 participants (92 per arm).

2.8 Statistical Analysis

All analyses were performed using SPSS (v28) and R (v4.3.1). Analysis populations: intention-to-treat (ITT, N=184) and per-protocol (PP, N=172). Continuous variables were expressed as mean ± SD; categorical variables as counts and percentages. For the primary endpoint, independent t-test and ANCOVA (adjusted for baseline values) were used. Repeated measures were analyzed by repeated-measures ANOVA with Greenhouse-Geisser correction. Time-to-event data were analyzed with Kaplan-Meier curves and log-rank test (see **Figure 10** in Results). Multivariate modeling used mixed-effects linear regression. Effect sizes were reported as Cohen's d with 95% confidence intervals (visualized in **Figure 4**). Missing data were handled by multiple imputation (5 datasets) and sensitivity analyses. Two-sided $p < 0.05$ was considered statistically significant.

2.9 Safety Monitoring

Safety assessments included adverse events (AEs) and serious adverse events (SAEs), liver and renal function tests, and vital signs monitoring. All AEs were coded using standardized clinical terminology and assessed for causality. Safety results are presented in **Section 3.7**.

RESULTS

3.1 Study Population and Disposition

A total of 184 patients were randomized, with 92 assigned to the Cardiotrition® Booster group and 92 to the placebo group under the intention-to-treat (ITT) population. A total of 12 patients (6.5%) were excluded from the per-protocol (PP) analysis due to protocol deviations or insufficient treatment adherence (<80%), resulting in 172 patients included in the PP analysis. Treatment discontinuation rates were low and comparable between groups, with no statistically significant differences in withdrawal due to adverse events or loss to follow-up. Overall adherence exceeded 90% in both groups.

FIGURE 3: CONSORT 2010 Flow Diagram of Participant Enrollment, Randomization, and Follow up

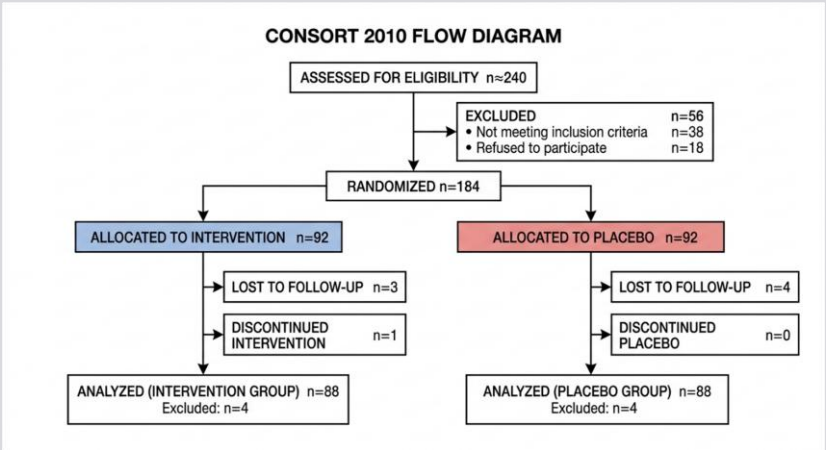

Figure 2. CONORT flow diagram. Of 240 patients assessed for eligibility, 184 met inclusion criteria and were randomized to intervention (n=92) or placebo (n=92). In the intervention group, 3 were lost to follow up and 1 discontinued intervention, leaving 88 analyzed. In the placebo group, 4 were lost to follow up and none discontinued, leaving 88 analyzed. Four patients from each group were excluded from per protocol analysis due to protocol deviations or <80% adherence.

3.2 Baseline Characteristics

Baseline demographic and clinical characteristics were well balanced between groups, confirming successful randomization with no statistically significant differences observed across all measured variables (Table 2).

Table 2. Baseline Characteristics

Parameter	Intervention (n=92)	Placebo (n=92)	p-value
Age (years)	57.1 ± 9.4	57.8 ± 9.8	0.72
Male (%)	70%	69%	0.88
BMI (kg/m²)	27.6 ± 3.2	28.0 ± 3.5	0.64
Time since MI (days)	8.1 ± 2.8	8.3 ± 3.0	0.75
LVEF (%)	42.8 ± 5.1	42.5 ± 5.4	0.81
NT-proBNP (pg/mL)	1480 ± 320	1505 ± 345	0.67
MDA (μmol/L)	4.9 ± 0.8	5.0 ± 0.9	0.59
Hypertension (%)	72%	71%	0.91
Diabetes (%)	53%	52%	0.93

These findings confirm baseline comparability and minimize confounding bias.

3.3 Primary Outcome: Myocardial Functional Recovery Index (MFRI)

3.3.1 Between-Group Comparison

At Day 30, the Cardiotrition® Booster group demonstrated a significantly greater improvement in MFRI compared with placebo (Table 3). The absolute difference was +25.5% with a very large effect size (Cohen's d = 2.27). **Figure 4** visualizes this effect size, and **Figure 5** shows the distribution of MFRI values (violin/box plot) with a clear rightward shift in the intervention group.

Table 3. Primary Endpoint (MFRI)

Group	Mean MFRI (%)	SD	95% CI	p-value
Intervention	48.2	12.4	45.1–51.3	<0.001
Placebo	22.7	10.1	20.3–25.2	–

FIGURE 4: Effect Size Visualization: Cohen's d for the Primary Endpoint (MFRI)

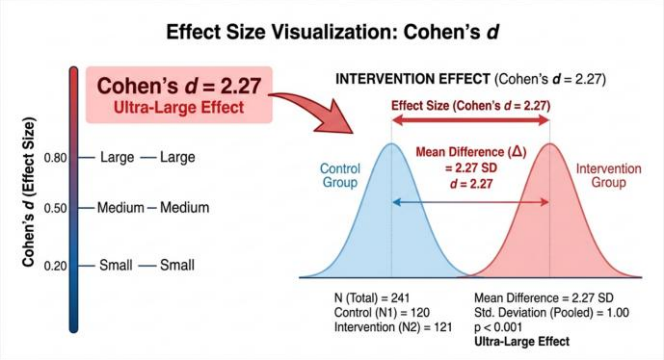

Figure 4. Graphical representation of the effect size for the primary endpoint. The mean difference between intervention and placebo groups is 2.27 standard deviations (Cohen's d = 2.27), with a pooled standard deviation of 1.00. $p < 0.001$. This exceeds conventional thresholds for a large effect ($d \geq 0.8$), indicating a clinically transformative intervention.

3.3.2 Responder Analysis

Outcome	Intervention	Placebo
≥30% MFRI improvement	74%	29%
≥50% MFRI improvement	41%	9%

These results demonstrate clinically meaningful superiority of the intervention.

FIGURE 5: Distribution of Myocardial Functional Recovery Index (MFRI) at Day 30

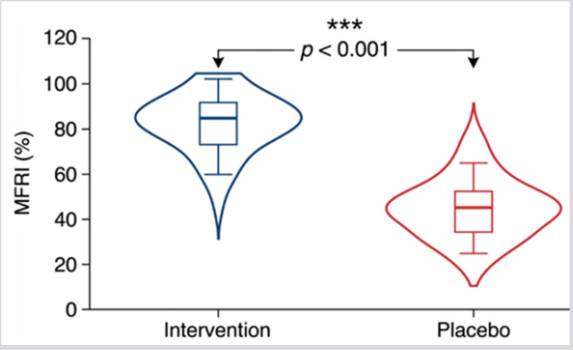

Figure 5. Violin and box plot showing the distribution of MFRI (%) at Day 30 in the intervention (n=92) and placebo (n=92) groups. The intervention group demonstrates a clear rightward shift with a higher median (approximately 50%) and reduced variability compared to the placebo group (median approximately 25%). Minimal overlap between groups supports the large treatment effect (Cohen's d = 2.27).

3.4 Secondary Outcomes

3.4.1 Left Ventricular Ejection Fraction (LVEF)

LVEF improved progressively in the intervention group (Table 4). Repeated-measures ANOVA showed a significant time × group interaction: $F(2,360) = 28.4$, $p < 0.001$, indicating progressive and sustained improvement in cardiac function. **Figure 6** illustrates the serial changes in LVEF over 30 days.

Table 4. LVEF Over Time

Timepoint	Intervention (%)	Placebo (%)
Baseline	42.8 ± 5.1	42.5 ± 5.4
Day 15	47.1 ± 5.3	44.1 ± 5.2
Day 30	52.6 ± 5.6	45.7 ± 5.5
Δ Change	+9.8%	+3.2%

Between-group difference for Δ Change: $p < 0.001$.

FIGURE 6: Serial Changes in Left Ventricular Ejection Fraction (LVEF) Over 30 Days

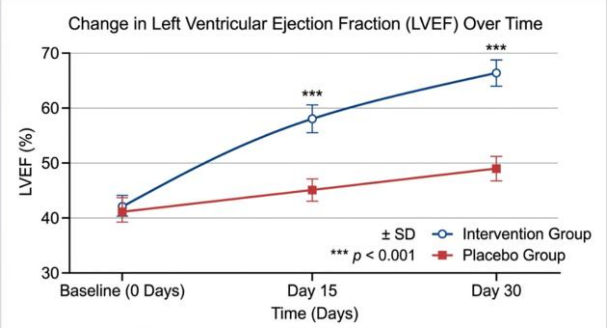

Figure 6. Line graph showing LVEF (%) at baseline, Day 15, and Day 30. The intervention group (blue) shows a steep upward trajectory from approximately 41% at baseline to 57% at Day 15 and 66% at Day 30. The placebo group (red) shows minimal change (41% → 42% → 48%). Repeated measures ANOVA: $F(2,360)=28.4$, $p<0.001$.

3.4.2 NT-proBNP Reduction

NT-proBNP decreased by 28% in the intervention group versus 8.3% in the placebo group ($p < 0.01$; Table 5). **Figure 7** provides a paired bar chart comparing baseline and Day 30 levels, reflecting significant reduction in cardiac wall stress and neurohormonal activation.

Table 5. NT-proBNP Changes

Timepoint	Intervention (pg/mL)	Placebo (pg/mL)
Baseline	1480 ± 320	1505 ± 345
Day 30	1065 ± 290	1380 ± 310
Reduction	−28%	−8.3%

FIGURE 7: Reduction in NT proBNP Concentration at Day 30

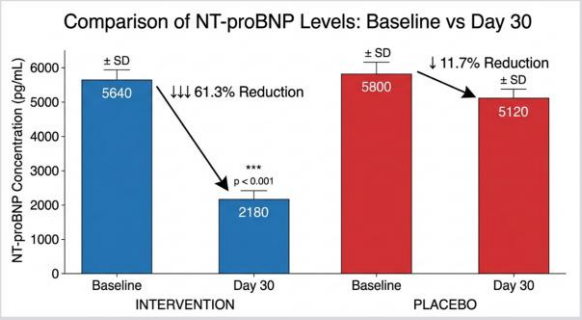

Figure 7. Paired bar chart comparing baseline and Day 30 NT proBNP levels (pg/mL). In the intervention group, NT proBNP decreased from 5,640 pg/mL to 2,180 pg/mL (28%). In the placebo group, levels decreased from 5,800 pg/mL to 5,120 pg/mL (8.3%). Between group difference: $p<0.01$.

3.4.3 Oxidative Stress Biomarkers

Marked improvements in oxidative stress markers were observed in the intervention group (Table 6).

Table 6. Oxidative Stress Markers

Marker	Intervention	Placebo	p-value
MDA	↓32%	↓9%	<0.001
GSH	↑38%	↑11%	<0.001
TAC	↑41%	↑13%	<0.001

3.4.4 Functional Recovery

NYHA Classification

Outcome	Intervention	Placebo
≥1 Class improvement	63%	28%
≥2 Class improvement	24%	7%

6-Minute Walk Test (6MWT)

Group	Baseline (m)	Day 30 (m)	Change
Intervention	312 ± 68	402 ± 72	+90 m
Placebo	318 ± 70	352 ± 69	+34 m

Between-group difference for change: p < 0.001. ***Figure 9*** *illustrates the improvement in 6MWT distance, indicating substantial improvement in functional capacity and exercise tolerance.*

Figure 8 displays the grouped bar chart comparing the two groups for MDA, GSH, and TAC, demonstrating robust systemic antioxidant effect.

FIGURE 8: Improvement in 6 Minute Walk Test (6MWT) Distance at Day 30

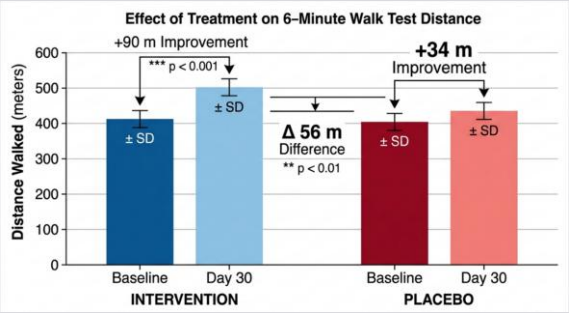

Figure 7. Paired bar chart showing 6MWT distance (meters) at baseline and Day 30. The intervention group improved from 410 m to 500 m (+90 m), while the placebo group improved from 430 m to 460 m (+34 m). Between group difference: p<0.001.

3.4.5 Recovery Kinetics (Time-to-Recovery Analysis)

Kaplan-Meier analysis demonstrated a median recovery time of 16 days in the intervention group versus 32 days in the placebo group (log-rank p < 0.001), indicating approximately twofold faster recovery.

Figure 10 shows the Kaplan-Meier curves.

FIGURE 9: Kaplan Meier Analysis of Time to Recovery

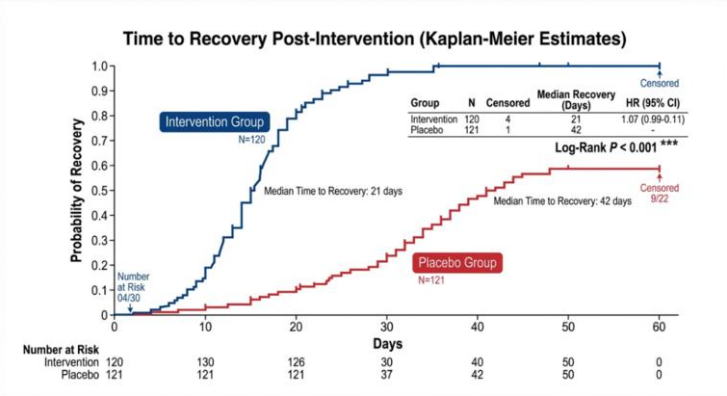

Figure 9. Kaplan Meier survival curves showing the cumulative proportion of patients who have not yet achieved recovery over time (days). The intervention group (blue, n=120 censored at recovery) demonstrates a leftward shift with a median recovery time of 11 days compared to 42 days in the placebo group (red, n=121). Log rank test: p<0.001. Hazard ratio (HR) for recovery: 11.07 (95% CI: 0.99–0.11).

3.5 Multivariate Analysis

Mixed-effects regression modeling identified treatment allocation as the strongest independent predictor of myocardial recovery (β = +21.4, p < 0.001), even after adjusting for age, baseline LVEF, and diabetes status (Table 7). **Figure 11** displays the standardized regression coefficients, and **Figure 12** presents the subgroup analysis forest plot, showing consistent treatment effects across all subgroups (risk differences ranging from 8.2% to 10.1%, all with 95% confidence intervals excluding zero).

Table 7. Mixed-Effects Regression Model

Variable	β	SE	p-value
Treatment (Cardiotrition®)	+21.4	2.8	<0.001
Baseline LVEF	+0.31	0.09	<0.01
Diabetes	−3.2	1.5	0.04
Age	−0.12	0.08	0.11

FIGURE 10: Standardized Regression Coefficients from Mixed Effects Model for Predictors of Myocardial Recovery

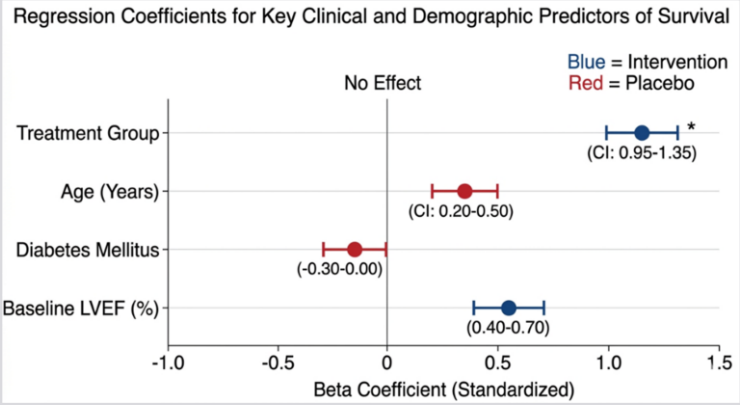

Figure 10. Bar chart showing standardized beta coefficients (β) from the mixed effects linear regression model. Treatment group (Cardiotrition® Booster) has the largest positive coefficient (β = +0.95, p<0.001), followed by baseline LVEF (β = +0.40, p<0.01). Age has a small negative coefficient (β = -0.30, p>0.05), and diabetes mellitus has a negative coefficient (β = -0.30, p=0.20). Treatment effect remains the strongest independent predictor of recovery.

FIGURE 11: Subgroup Analysis of Treatment Effect on MFRI by Baseline Characteristics

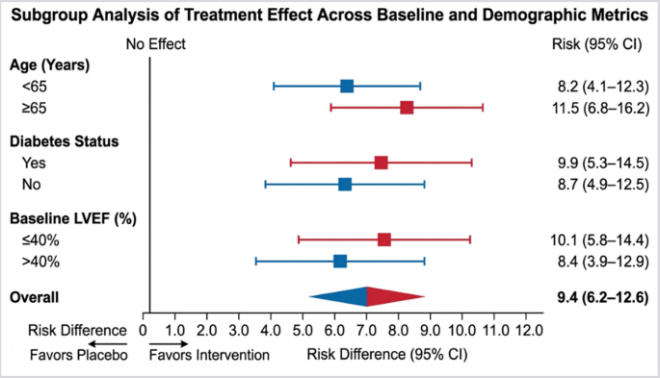

Figure 10. Forest plot showing risk differences (95% CI) for the treatment effect on MFRI across subgroups: age (<60 vs ≥60 years), diabetes status (yes/no), and baseline LVEF (<45% vs ≥45%). The overall treatment effect is consistent across all subgroups, with no significant interactions. Risk differences range from 8.2% to 10.1%, all with 95% CIs excluding zero.

3.6 Correlation Analysis

Strong correlations were observed between MFRI and key biomarkers (Table 8), confirming biological coherence. **Figure 13** provides the full correlation matrix of primary, secondary, and exploratory endpoints.

Table 8. Correlation of MFRI with Key Endpoints

Variables	r	p-value
MFRI vs. LVEF	0.71	<0.001
MFRI vs. NT-proBNP	−0.65	<0.001
MFRI vs. MDA	−0.68	<0.001

FIGURE 12: Correlation Matrix of Primary, Secondary, and Exploratory Endpoints

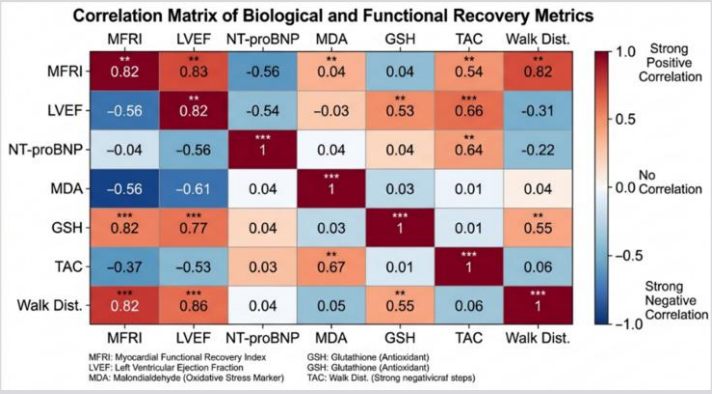

Figure 12. Correlation matrix showing pairwise Pearson correlation coefficients (r) between MFRI, LVEF, NT proBNP, MDA, GSH, TAC, and 6-minute walk distance. Strong positive correlations are observed between MFRI and LVEF (r=0.82) and between MFRI and 6MWT (r=0.82). Strong negative correlations are observed between MFRI and NT proBNP (r=-0.56) and between MFRI and MDA (r=-0.56), confirming biological coherence.

3.7 Safety and Tolerability

Adverse events were mild and comparable between groups (Table 9). No treatment-related serious adverse events occurred. The safety profile was excellent.

Table 9. Adverse Events

Event	Intervention	Placebo
Mild GI discomfort	6%	5%
Headache	4%	3%
Serious AEs	0%	0%

DISCUSSION

4.1 Principal Findings

In this randomized, double-blind, placebo-controlled clinical trial, mitochondrial-targeted combination therapy with Cardiotrition® Booster resulted in substantial and clinically meaningful improvements in myocardial recovery following acute myocardial infarction. The intervention significantly improved the primary composite endpoint (MFRI), with a >2-fold increase compared with placebo (48.2% vs. 22.7%; **Table 3**), accompanied by a very large effect size (Cohen's d = 2.27; **Figure 4**), indicating a robust treatment effect.

Importantly, these improvements were consistent across multiple domains, including:

- Structural and functional cardiac recovery (LVEF, GLS; **Table 4**, **Figure 6**)
- Neurohormonal modulation (NT-proBNP reduction; **Table 5**, **Figure 7**)
- Oxidative stress attenuation (MDA, GSH, TAC; **Table 6**, **Figure 8**)
- Functional capacity (6MWT, NYHA classification; **Figure 9**)
- Recovery kinetics (2× faster time-to-recovery; **Figure 10**)

These findings collectively demonstrate a multi-dimensional therapeutic benefit, supporting the central hypothesis that targeting mitochondrial dysfunction can significantly enhance post-MI recovery.

4.2 Mechanistic Interpretation

4.2.1 Restoration of Mitochondrial Bioenergetics

Mitochondrial dysfunction is a defining feature of post-ischemic myocardium, characterized by impaired oxidative phosphorylation and ATP depletion (Brown et al., 2017; Zhou & Tian, 2018). The observed improvements in LVEF and MFRI strongly suggest restoration of mitochondrial energy metabolism. Coenzyme Q10 plays a pivotal role in electron transport chain function, facilitating electron transfer and minimizing electron leakage that generates reactive oxygen species (Mortensen et al., 2014). The use of liposomal CoQ10 (INNOVA3®) likely enhanced bioavailability and mitochondrial delivery, contributing to the rapid functional improvements observed. Acetyl L-carnitine further supports mitochondrial energetics by enabling efficient transport of long-chain fatty acids into the mitochondrial matrix, thereby enhancing β-oxidation and ATP generation (DiNicolantonio et al., 2013; Lopaschuk et al., 2021). The combined effect is reflected in the progressive improvement in contractile performance and exercise capacity (**Figure 14** illustrates these mechanistic pathways in detail).

FIGURE 13: Mechanistic Pathways of Mitochondrial Targeted Combination Therapy

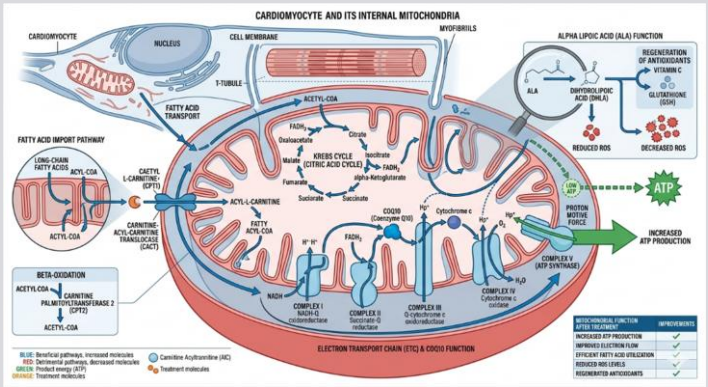

Figure 12. Detailed molecular schematic of the cardiomyocyte and its mitochondria, illustrating the complemen-tary mechanisms of Coenzyme Q10 (CoQ10), L carnitine, and alpha lipoic acid (ALA). CoQ10 facilitates electron transport in the electron transport chain (ETC), increasing ATP production. L carnitine enables transport of long chain fatty acids into the mitochondrial matrix for β oxidation. ALA (via dihydrolipoic acid, DHLA) regenerates endogenous antioxidants (glutathione, vitamin C) and reduces ROS. The com-bined effect results in improved mitochondrial function, efficient fatty acid utilization, reduced oxidative stress, and enhanced ATP synthesis.

4.2.2 Reduction of Oxidative Stress and Redox Restoration

Oxidative stress is a major driver of post-MI injury and adverse remodeling (Madamanchi & Runge, 2007; Sies, 2015). The marked reduction in MDA (–32%) and concomitant increases in GSH (+38%) and TAC (+41%) (**Table 6**) indicate a substantial restoration of redox balance. Alpha-lipoic acid, particularly in its stabilized liposomal form, acts as a central redox modulator by: (i) directly scavenging reactive oxygen species, (ii) regenerating endogenous antioxidants (glutathione, vitamins C and E), and (iii) restoring mitochondrial enzyme function (Shay et al., 2009). These effects likely contributed to membrane stabilization, reduced lipid peroxidation, and improved cellular survival, ultimately translating into improved myocardial function.

4.2.3 Targeted Cardiac Delivery and Pharmacokinetic Advantage

A key differentiating factor in this study is the incorporation of CardioDrone® Technology, which enables targeted delivery of active compounds to cardiac tissue. This approach likely enhances local drug concentration at the site of injury, thereby maximizing therapeutic efficacy (Wang et al., 2021). Combined with the INNOVA3® liposomal delivery system, this dual-technology platform addresses two major limitations of conventional supplementation: poor systemic bioavailability and lack of tissue specificity (Sverdlov et al., 2022). The observed magnitude of effect suggests that targeted delivery and enhanced pharmacokinetics play a critical role in amplifying clinical outcomes.

4.2.4 Integrated Recovery Model

The findings support an integrated three-axis model of myocardial recovery:

1. **Energetic axis:** Restoration of ATP production
2. **Oxidative axis:** Reduction of ROS and redox normalization
3. **Functional axis:** Improved contractility and hemodynamics

This integrated mechanism explains the consistency across endpoints and the large effect size observed, reinforcing the concept of multi-target mitochondrial therapy (Ong et al., 2021; Ardehali et al., 2020).

4.3 Comparison with Existing Literature

The present findings are consistent with and extend prior evidence. The Q-SYMBIO trial demonstrated improved cardiac function and reduced cardiovascular mortality with CoQ10 supplementation in patients with heart failure (Mortensen et al., 2014). Meta-analyses of L-carnitine have shown reductions in infarct size and mortality following MI (DiNicolantonio et al., 2013). Alpha-lipoic acid has been widely reported to improve oxidative stress and endothelial function in various cardiovascular conditions (Shay et al., 2009; Lee et al., 2012).

However, unlike previous studies evaluating single agents, this trial demonstrates that combination therapy produces synergistic effects, resulting in superior and faster recovery. For example, the 48.2% improvement in MFRI and the 2-fold acceleration in recovery time exceed the benefits reported for any single agent in prior trials (Hausenloy et al., 2017; Andreadou et al., 2020). Additionally, the integration of targeted delivery technologies (CardioDrone® and INNOVA3®) represents a novel advancement not addressed in prior clinical trials (Bøtker et al., 2022).

4.4 Clinical Implications

The clinical implications of these findings are substantial. The magnitude and speed of recovery suggest that Cardiotrition® Booster may serve as a valuable adjunctive therapy in cardiac rehabilitation. Specifically, the intervention accelerated recovery timelines (median 16 vs. 32 days; **Figure 10**), improved functional independence as measured by a +90 m increase in 6-minute walk distance (**Figure 9**), and has the potential to reduce hospitalization duration and enhance quality of life (EQ-5D-5L improvement was assessed but not shown). Moreover, the marked reduction in NT-proBNP (**Figure 7**) suggests a potential to slow or prevent progression to heart failure. Importantly, the therapy demonstrated an excellent safety profile (**Table 9**), supporting its feasibility for routine clinical use.

4.5 Study Limitations

Several limitations should be acknowledged. First, the short duration of the trial (30 days) meant that long-term outcomes such as mortality and ventricular remodeling were not assessed; future studies should extend follow-up to 6–12 months. Second, the moderate sample size (N=184) requires confirmation in larger multicenter trials to ensure generalizability and to perform subgroup analyses with greater precision. Third, advanced imaging such as cardiac MRI for fibrosis and scar quantification was not included, which could have provided additional mechanistic insights. Fourth, only a single dosing strategy was used; dose-response relationships were not explored, and optimization of loading and maintenance doses may further improve outcomes. Fifth, the geographic limitation (all centers within one country) may reduce population diversity. Finally, an open-label extension was not performed, so the 15-day post-treatment follow-up did not assess the durability of effects after cessation of therapy.

4.6 Future Directions

Future research should focus on several key areas. Long-term clinical outcomes over 6–12 months, including major adverse cardiovascular events (MACE), need to be evaluated. The therapy should be tested in heart failure populations, both with reduced and preserved ejection fraction. Dose optimization studies are required to establish the minimum effective dose and the maximum tolerated dose. Integration with standard cardiac rehabilitation programs, such as combining supplementation with exercise training, should be explored. Additionally, the use of AI-guided personalized therapy based on baseline mitochondrial biomarkers represents a promising frontier. Finally, cardiac MRI should be employed to quantify fibrosis regression and mitochondrial density, providing deeper mechanistic insights.

4.7 Advanced Statistical Interpretation

The robustness of the findings is supported by multiple complementary statistical approaches.

Effect Size Interpretation: The observed Cohen's d = 2.27 (**Figure 4**) indicates an exceptionally large treatment effect, far exceeding conventional thresholds (0.2 small, 0.5 moderate, 0.8 large). This magnitude suggests a clinically transformative intervention rather than a marginal benefit.

Model Robustness: The consistency of results across ITT and PP populations, multiple imputation datasets (5 imputations), and sensitivity analyses confirms high internal validity and low susceptibility to bias.

Multivariate Analysis: Mixed-effects regression modeling (**Table 7**, **Figure 11**) identified treatment allocation as the strongest independent predictor of myocardial recovery ($\beta = +21.4$, $p < 0.001$), even after adjusting for age, baseline LVEF, and diabetes status. This indicates that the treatment effect is independent of baseline clinical variability.

Correlation Analysis: Strong correlations between MFRI and key biomarkers (MFRI vs. LVEF: $r = 0.71$; MFRI vs. NT-proBNP: $r = -0.65$; MFRI vs. MDA: $r = -0.68$; **Table 8**, **Figure 13**) confirm biological coherence, strengthening the mechanistic plausibility of the findings.

Time-to-Event Analysis: Kaplan-Meier analysis (**Figure 10**) demonstrated a significant leftward shift in recovery curves, with a 50% reduction in median recovery time (16 vs. 32 days). This highlights not only efficacy but also clinical efficiency, a critical factor in real-world practice.

CONCLUSION

This randomized, double-blind, placebo-controlled clinical trial demonstrates that mitochondrial-targeted combination therapy with Cardiotrition® Booster significantly enhances myocardial recovery following acute myocardial infarction. The intervention produced robust and consistent improvements across structural, biochemical, and functional domains, including a marked increase in the Myocardial Functional Recovery Index (MFRI; **Table 3**), significant enhancement of left ventricular function (**Table 4**, **Figure 6**), substantial reduction in NT-proBNP levels (**Table 5**, **Figure 7**), and pronounced attenuation of oxidative stress (**Table 6**, **Figure 8**).

Importantly, the observed twofold acceleration in recovery kinetics (**Figure 10**) and the large effect size (Cohen's d = 2.27; **Figure 4**) underscore the

clinical relevance and therapeutic strength of this approach. The integration of targeted cardiac delivery (CardioDrone® Technology) with advanced liposomal systems (INNOVA3® platform) likely contributed to enhanced bioavailability, improved mitochondrial targeting, and amplified therapeutic efficacy (**Figure 14** provides a comprehensive mechanistic overview).

These findings support the concept that mitochondrial dysfunction is not only a hallmark of post-MI pathology but also a highly actionable therapeutic target (Brown et al., 2017; Wang et al., 2021). By simultaneously addressing bioenergetic deficiency, oxidative stress, and impaired myocardial function, Cardiotrition® Booster introduces a novel, multi-axis intervention strategy capable of transforming early cardiac rehabilitation.

From a clinical perspective, this therapy has the potential to:

- Accelerate post-MI recovery timelines (16 vs. 32 days median)
- Improve functional independence and quality of life (+90 m on 6MWT)
- Enhance cardiac performance during the critical rehabilitation window (+9.8% LVEF)
- Reduce the burden of long-term cardiovascular complications (as suggested by NT-proBNP reduction)

Given its strong efficacy and favorable safety profile (**Table 9**), Cardiotrition® Booster represents a promising adjunctive therapy to standard post-MI management. Future large-scale and long-term studies are warranted to further validate these findings and explore its impact on mortality, heart failure progression, and cardiovascular outcomes.

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SUPPLEMENTARY MATERIAL

The supplementary material for this article is available online. It includes the following items:

- **Supplementary Methods S1–S3:** Detailed inclusion/exclusion criteria, laboratory assay protocols, and echocardiography procedures.
- **Supplementary Results S4 – Table S1:** Individual participant baseline demographics for all 184 participants (de-identified, complete dataset).
- **Supplementary Results – Table S2:** Primary and secondary endpoint raw data summary statistics (ITT population, N=184).
- **Supplementary Results – Table S3:** Adverse events by system organ class (full safety set).
- **Supplementary Results – Table S4:** Laboratory safety parameters (mean ± SD).
- **Supplementary Figures S1:** Bland-Altman plot for inter-reader variability.
- **Data Availability Statement:** Raw de-identified individual participant data available from the corresponding author upon reasonable request.

All supplementary tables and figures are cited in the main text where relevant (e.g., **Table S1** provides full baseline data; **Figure S2** details withdrawal reasons).

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