Research Article

Cardioprotective Effects of Coenzyme Q10 Supplementation on Patients with ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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Abstract

Background: We assessed the potential efficacy of Coenzyme Q10 (CoQ10) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI).

Methods: Seventy STEMI patients who presented ≤12 hours after the onset of symptoms and were scheduled for PPCI were randomly assigned to the standard treatments plus CoQ10 or placebo. In the intervention group, CoQ10, as an oral capsule at a dose of 400 mg, was loaded immediately before PPCI and continued at 200 mg twice daily for 28 days. The control group received a matching placebo, similarly. The study endpoints were the proportion of patients with complete myocardial reperfusion, defined as thrombolysis in myocardial infarction (TIMI) flow and myocardial blush grade (MBG) 3 at the end of PPCI, the proportion of patients with complete ST-segment elevation resolution (≥70%) assessed 60 minutes after PPCI, the plasma levels of creatine kinase myocardial band isoenzyme (CK-MB) and troponin I (TnI) at 12, 24, 48, and 72 hours after PPCI, and left ventricular ejection fraction (LVEF) at day 28.

Results: The study groups were comparable regarding baseline clinical and procedural characteristics. The proportion of patients with TIMI flow grade 3, MBG 3, and complete ST resolution after completion of PPCI was similar between the groups. Whereas at all-time points after PPCI (12, 24, 48, and 72 hours), the plasma levels of CK-MB and TnI were significantly lower in the CoQ10 group than in the control group. Further, at day 28, CoQ10-treated patients exhibited better LVEF than placebo-treated patients, and the proportion of patients with LVEF less than 50% was lower in the intervention group than in the control group.

Conclusion: Our study provided evidence that CoQ10 supplementation might reduce myocardial ischemia-reperfusion injury after PPCI and help to preserve left ventricular function. However, further studies are required to validate these results.

Introduction

Over the last two decades, mortality in acute myocardial infarction decreased significantly.[1] It is now clear that timely and effective coronary reperfusion modalities using thrombolysis, primary percutaneous coronary intervention (PPCI), or coronary artery bypass grafting (CABG) prevent loss of contractile myocardial muscle mass, decrease the infarct size, prevent post-ischemic heart failure, and improve survival.[2] Nonetheless, reperfusion therapy by itself may result in a phenomenon called myocardial ischemia-reperfusion injury that paradoxically reduces the beneficial effects of myocardial reperfusion and worsens clinical outcomes after an acute myocardial infarction.[3] Given the detrimental effects of this phenomenon, developing effective strategies to protect cardiomyocytes against myocardial ischemia-reperfusion injury can improve the prognosis of patients with myocardial infarction undergoing reperfusion. A variety of pharmacological agents, such as cyclosporine-A, calcium channel blockers, β-blockers, statins, inhibitors of neutrophils, nitrates, adenosine receptor agonists, inhibitors of the renin–angiotensin system, endothelin

receptor antagonists, glucose modulators, Na$^+$/H$^+$ exchange inhibitors, and anti-apoptotic agents have been investigated that despite the convincing experimental evidence, the translation to the clinical setting has been disappointing.[4,5] Therefore, efforts to find a therapeutic approach to protect against myocardial ischemia-reperfusion injury are still ongoing.

The pathogenesis of myocardial ischemia-reperfusion injury is multifactorial, involving the interaction of a number of pathophysiological mechanisms. Cellular calcium loading, mitochondrial damage, oxidative stress injury, and overactive inflammatory responses are possible pathological mechanisms principally involved in the pathogenesis of reperfusion injury.[6] The level of myocardial tissue oxygenation increases following the restoration of blood flow, which is associated with a sudden burst of reactive oxygen species (ROS) production; toxic accumulation of ROS generates rapid and severe damage to protein, lipid, nucleic acid, and other macromolecules, which can ultimately lead to acute, irreversible myocardial cell death.[7] Excess ROS triggers harmful inflammatory responses within the myocardium, inducing cytokines and chemokine production with infiltration of immune system cells to the infarct zone.[8] Ultimately, the imbalance between pro-inflammatory and anti-inflammatory responses elicited by ischemia and reperfusion can induce cardiomyocyte death and myocardial injury.[9] Oxidative stress also, by impairing membrane fluidity and increasing calcium permeability, which results in excessive cytoplasmic and mitochondrial calcium, can lead to mitochondrial dysfunction and activation of apoptosis signaling pathways.[10] Accordingly, it is not surprising that, recently, pharmacological interventions targeting mitochondrial dysfunction, oxidative stress, and inflammation are being extensively evaluated as potential cardioprotective interventions against myocardial ischemia-reperfusion injury. However, while preclinical studies showed promising results with these agents, the findings from human clinical studies have been yet mixed and inconclusive.[11,12]

Coenzyme Q10 (CoQ10), the only endogenous lipid-soluble antioxidant, has an essential role in electron and proton transfer during oxidative phosphorylation and cellular adenosine triphosphate (ATP) generation. It also acts as a potent antioxidant not only in mitochondria but also in other cell compartments.[13] Besides its antioxidant activity that diminishes oxidative damage, CoQ10 also has the ability to improve endothelial function,[14] palliate proinflammatory responses,[15] restore intracellular calcium hemostasis, and decrease cellular apoptosis.[16] Since the heart is a very active organ that requires a lot of energy, it normally contains high levels of CoQ10.[17] Diminished CoQ10 levels in both myocardial tissue and serum have been noted in patients with cardiovascular diseases that are linked to the severity of these diseases and worse clinical outcomes.[18-20] The potential cardioprotective effects of CoQ10 have been widely investigated in both animal and

human studies. The results of these studies have validated that exogenous CoQ10 supplementation can be helpful in the prevention and treatment of a variety of cardiovascular diseases, such as congestive heart failure, cardiomyopathy, ischemic heart disease, and acute coronary syndrome.[21,22] It is well known that myocardial CoQ10 depletion occurs during ischemia and reperfusion, which has a negative impact on post-myocardial infarction outcomes.[23-25] This suggests that restoring tissue CoQ10 deficiency in the myocardium by exogenous administration may prevent the cardiac structural and functional sequel of ischemia-reperfusion injury. Emerging evidence has also indicated that exogenous administration of CoQ10 can have a protective effect against myocardial ischemia-reperfusion injury.[26,27] This hypothesis was examined in both animal and human research, with particularly encouraging results from experimental research.[27-31] Given that, to date, there is no randomized controlled trial specifically evaluating the effectiveness of CoQ10 supplementation in patients with ST-segment elevation myocardial infarction (STEMI) undergoing PPCI, we designed and conducted this study to assess whether administration of CoQ10 can improve myocardial reperfusion after the procedure, reduce the amount of myocardial ischemia-reperfusion injury, and preserve heart function in this patient population.

Methods
Study design
The present study was an interventional, single-center, randomized, double-blind, parallel-group, active-controlled clinical trial conducted from November 2021 to August 2022 in a tertiary referral hospital in the West of Iran. The study protocol was conducted in line with the 2013 Helsinki Declaration, and ethical approval was got from the local Research Ethics Committee (License number: IR.UMSHA.REC.1400.623). Before the enrolment began, the trial was registered at the Iranian Registry of Clinical Trials (www.irct.ir/trial/60026) with the trial Number: IRCT20120215009014N407. Informed consent was got from the patients or their legally authorized representatives before beginning any intervention.

Patient enrollment
During the study period, women and men aged between 18 and 80 years old with a diagnosis of STEMI, defined as chest pain lasting longer than 30 minutes associated with ST-segment elevation of ≥ 0.1 mV in 2 or more contiguous electrocardiographic leads, who presented ≤12 hours after the onset of symptoms and scheduled for PPCI were screened for participation in the trial. All patients had elevation serum creatine kinase myocardial band isoenzyme (CK-MB) and/or troponin I (TnI). Patients are not eligible for participation if they have any following criteria: pre-hospital fibrinolytic therapy, cardiac arrest, cardiogenic shock at the time of presentation, left bundle-branch block, moderate to severe mitral regurgitation, previous myocardial infarction or cardiac revascularization, history

of any cardiac surgery, concurrent inflammatory condition, infectious, or malignant disease, a history of renal or hepatic insufficiency (serum ALT or total bilirubin >3 times of the normal upper limit and estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2}), any serious medical comorbidity with reduced short-term prognosis, history of or known allergy or intolerability to the study medication, high probability of being unavailable for follow-up visits, and pregnancy or breastfeeding.

Intervention

Patients in both groups received standard medical treatments pre- and post-PPCI as stated in current practice guidelines.[32] All the study patients received a loading dose of antiplatelet drugs (325 mg aspirin and 600 mg clopidogrel or 180 mg ticagrelor) in the emergency room and were intravenously injected with unfractionated heparin (70 U/kg) intra-procedural. After the procedure, all patients received dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (clopidogrel or ticagrelor), and if not contraindicated, they received statins, β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) as recommended in current guidelines. Coronary angiography and stent implantation were performed according to standard practice by two experienced interventional cardiologists.[32] The procedure was performed from the right femoral or the radial route at the operator's discretion. According to the complexity of vascular lesions and thrombotic load, intracoronary GP IIb/IIIa inhibitors were administered during or after catheterization at the discretion of the interventional cardiologists.

Apart from the standard treatment, in patients randomized to the intervention group, CoQ10 at a dose of 400 mg was loaded before the procedure, and afterward, CoQ10 was prescribed at a dose of 200 mg twice daily for 28 days. The control group received a matching placebo similarly. This dose was based on previous research suggesting that 200 mg twice a day is required to achieve a therapeutic blood level of CoQ10 (2.0–3.0 μg/mL).[33] To enhance participant's adherence to the study medications, during the study period, the patients were reminded through phone calls to take their treatment. Adherence to treatment was determined by counting the number of blisters returned at the end of the study and patients were considered adherent to treatment if they received at least 90% of the expected number of doses. The occurrence of adverse effects of the treatment was assessed by reporting spontaneously by the patient or in response to questions not addressed. All study patients were scheduled for follow-up 28 days after enrollment.

Efficacy Assessment

The patient's demographic and clinical characteristics and procedural, laboratory, angiographic, and ECG data were collected from the patients' database at baseline. The patients in both groups were followed up during hospitalization and within 28 days after enrolment. Pre- and post-PCI angiograms were analyzed by an experienced interventional cardiologist without knowledge of the patient group allocation. Thrombolysis in myocardial infarction (TIMI) flow grade, myocardial blush grade (MBG), and ST-segment elevation resolution were used to assess the effectiveness of myocardial reperfusion. TIMI flow score is a widely used qualitative angiographic parameter for the assessment of the extent of coronary blood flow in the culprit coronary. The flow in the infarct-related artery, as previously described,[34] was classified: Grade 0 (no perfusion), Grade 1 (penetration with no perfusion), Grade 2 (perfusion is partial), and Grade 3 (perfusion is complete). The MBG is another qualitative angiographic parameter that is used to describe the effectiveness of myocardial reperfusion. It is based on the visual assessment of contrast opacification of the myocardium supplied by the infarct-related artery and is graded as previously proposed by van' t Hof *et al.*[35]: Grade 0: no myocardial blush or contrast density, Grade 1: minimal myocardial blush or contrast density, Grade 2: moderate myocardial blush or contrast density, and Grade 3: normal myocardial blush or contrast density comparable with that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery. A 12-lead surface ECG was obtained before coronary reperfusion and then 60 minutes after the procedure to calculate the percentage of ST-segment elevation resolution. The percent of early ST-segment elevation resolution after the procedure was categorized based on Schroder's method as complete (≥70%), partial (30% to <70%), or absent (<30%).[36]

The amount of myocardial ischemia-reperfusion injury was assessed by the enzymatic method. For this, plasma levels of CK-MB and TnI were measured immediately before the procedure and again at 12, 24, 48, and 72 hours after the procedure. The diagnostic cutoff point for CK-MB was 5 ng/mL and for TnI was 0.4 ng/mL. Additionally, left ventricular ejection fraction (LVEF) on day 28, measured by two-dimensional echocardiography, was used to assess the change in left ventricular function after the intervention. Echocardiographic measurements at baseline and follow-up were performed by a single operator that was blinded to group allocations. The LVEF of less than 50% was considered the left ventricular systolic dysfunction (LVSD).

Primary and secondary clinical outcomes

The primary study endpoints were the proportion of patients with complete myocardial reperfusion, defined as TIMI flow grade 3 and MBG 3 at the end of PPCI, and the proportion of patients with complete ST-segment elevation resolution (≥70%) measured 60 minutes after the procedure. As secondary endpoints, the following outcomes were compared between the study groups: the serum levels of CK-MB and TnI at 12, 24, 48, and 72 hours after the procedure, the LVEF values at day 28, the proportion of

patients with LVSD at day 28, defined as LVEF less than 50%, and the incidence of the adverse effects.

Sample size calculation

According to the results of a study conducted by Basili *et al.*,[37] the mean (SD) myocardial perfusion index was 30.3 (8.0) and 21.3 (5.2) in the intervention and control groups, respectively. On the basis of these results, we arrived at a sample size of 28 for each group and a total sample size of 56 at 99% significance level and 98% statistical power. Anticipating a 20% loss to follow-up, we increased the sample size to a maximum of 70, of which 35 were randomly allocated to the placebo group, 35 to the intervention group.

Randomization and blinding

Patients who satisfied the inclusion and exclusion criteria were randomly assigned in a 1:1 ratio to either treatment with CoQ10 or placebo, using the block randomization method. The randomization and treatment allocation was conducted by a researcher with no relation to the study. The CoQ10 capsules were manufactured by Bonyad

Salamat Kasra, Tehran, Iran, and the placebo tablets with identical size, color, shape, taste, packaging, and labeling were prepared by the department of pharmaceutics of the School of Pharmacy at Hamadan University Medical Sciences. Both patients and investigators remained blinded to patient groupings throughout the study.

Statistical analyses

Data analysis was performed by IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, N.Y., USA). Intention-to-treat (ITT) analysis was conducted, which was defined as all patients who took at least one dose of the study drug and had at least one post-baseline efficacy assessment. The last value carried forward method (LOCF) was used to estimate missing data. The Kolmogorov-Smirnov test was performed to evaluate the normality of the continuous variable distribution. Normally distributed continuous variables were reported as mean ± standard deviation (SD), and non-normally distributed continuous data were expressed as median (interquartile range [IQR]). Categorical variables are reported as numbers and percentages. Normally distributed continuous variables
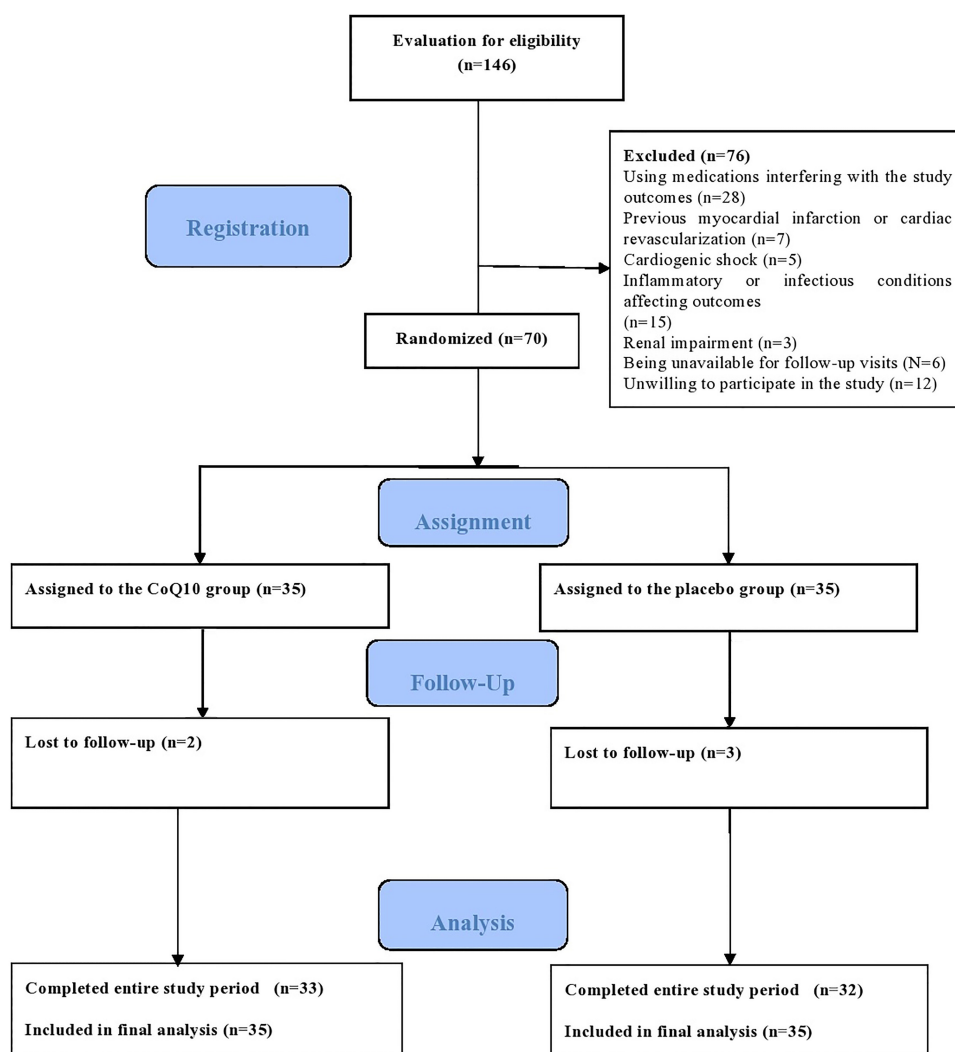

Figure 1. The study flow diagram.

were analyzed with Student's t-test, non-normally distributed continuous variables were analyzed with Mann–Whitney U test, and categorical variables were assessed by the chi-square test or Fisher exact test as appropriate. Repeated measures analysis of variance (ANOVA) was used to assess changes in serum values of variables with repeated measurement. Statistical significance was set at p-values ≤0.05. However, for the sake of five multiple comparisons (the pelasma levels of CK-MB and TnI), the significance level was corrected using Bonferroni's multiple testing method. We obtained a significance level of 0.010 for five comparisons. Accordingly, the p-values less than 0.010 based on Bonferroni's multiple-testing correction method were considered statistically non-significant.

Results
Demographics and baseline characteristics
A flowchart of the trial is shown in Figure 1. During the study period, 146 STEMI patients with indications for PPCI were assessed for enrolment. Of whom, 76 cases were excluded. Sixty-four patients did not satisfy the inclusion and exclusion criteria, and 12 eligible patients declined to participate in the study. Of the 70 patients who were enrolled, 35 patients were allocated to the CoQ10 group (intervention group) and 35 to the placebo group (control group). Two patients in the intervention group and three patients in the control group did not complete the 28-day follow-up; however, considering that all randomized subjects took at least one dose of the study drug and had at least one post-baseline efficacy assessment, all of them were included in the final analysis. The adherence rate was comparable in two groups (p-value= 1.00), as 94.3% of the patients in the intervention group and 92.9% patients in the control group were adherent to the study medications. The baseline demographic and clinical characteristics of patients in the treatment groups are displayed in Table 1. As shown, treatment groups were well-balanced in baseline characteristics. The mean age of the study population was 63.25 (ranged 45-75) years, and 71.4% of them were men. There was no significant difference between the treatment groups in terms of cardiovascular risk factors and the baseline systolic and diastolic blood pressure, heart rate, LVEF, biochemical data, and cardiac biomarkers levels. The mean pain-to-balloon time was 244.07±34.98 min, and the mean door-to-balloon time was 42.64±6.12 min, and there was no difference between the groups.

The treatment groups were also comparable concerning medication use on admission and discharge. In angiography, in 81.4% of the cases, the procedure was performed via the radial access site and in 18.6% via the

Table 1. Demographics and clinical characteristics of the Intention-to-Treat Population at Baseline.

Variable	CoQ10 treated-Group (35 patients)	Placebo treated-Group (35 patients)	p-value
Age, years, Mean±SD	61.85±8.27	64.65±7.45	0.142
BMI, (Kg/m²), Mean±SD	24.75±3.31	24.58±2.50	0.814
Sex (M/F), n (%)	26/9 (74.3/25.7)	24/11(68.6/31.4)	0.792
Related risk factors, n (%)			
Hypertension	20 (57.10)	18 (51.40)	0.811
Diabetes mellitus	8 (22.90)	9 (25.70)	1
Dyslipidemia	21(60.0)	20 (57.10)	1
Current smoker	11 (31.40)	16 (45.70)	0.326
Family history of coronary artery disease	8 (22.90)	11 (31.40)	0.592
Culprit lesion, n (%)			0.9
Left main	1 (2.90)	0 (0.0)	
Left anterior descending	16 (45.70)	16 (45.70)	
Left circumflex	6 (17.10)	5 (14.30)	
Right coronary artery	12 (34.30)	14 (40.0)	
Multivessel PCI, n (%)	11(31.40)	8 (22.90)	0.829
Vascular access, n (%)			
Radial	30(85.70)	27 (77.10)	0.54
Femoral	5 (14.30)	8 (22.90)	
Glycoprotein IIb/IIIa inhibitor use, n (%)	7 (25.0)	5 (14.30)	0.755
Thrombus aspiration, n (%)	6 (17.10)	3 (8.60)	0.477
Door-to-balloon time (minutes), Median (IQR)	40.00 (5.00)	40.00 (5.5)	0.995
Pain-to-balloon time (minutes), Median (IQR)	245.00 (50.00)	245.00 (25.00)	0.719
Ejection fraction,%, Median (IQR)	53.00 (7.00)	52.00 (5.00)	0.448
Systolic blood pressure (mmHg), Mean±SD	123.54±7.26	126.11±10.57	0.24
Diastolic blood pressure (mmHg), Mean±SD	73.22±6.06	72.40±5.04	0.536
Heart rate , Median (IQR)	77.00 (14.00)	76.00 (9.00)	0.948
Baseline laboratory findings			
Serum creatinine, (mg/dL), Mean±SD	1.05±0.23	0.99±0.09	0.174
CK-MB, (ng/mL), Mean±SD	47.74±6.85	52.42±7.47	0.08
Troponin I, (ng/mL), Mean±SD	6.61±7.68	5.31±4.59	0.392

Table 1 Continued.

Total cholesterol, (mg/dL), Median (IQR)	239.00 (58.00)	226.00 (60.00)	0.851
Triglyceride, (mg/dL), Median (IQR)	153.00 (37.00)	162.00 (35.00)	0.677
LDL cholesterol (mg/dL), Median (IQR)	105.00 (26.00)	108.00 (28.00)	0.716
HDL cholesterol, (mg/dL), Mean±SD	38.27±6.74	37.85±5.24	0.774
Fasting blood sugar, (mg/dL), Median (IQR)	112.00 (12.00)	111.00 (37.00)	0.972
Medications use on admission, n (%)			
On Aspirin	12 (34.30)	15 (42.90)	0.624
On ACEI treatment	11 (31.40)	13 (37.10)	0.802
On ARB treatment	6 (17.10)	5 (14.30)	1
On Beta blockers treatment	10 (28.60)	12 (34.30)	0.797
On CCB treatment	7 (20.00)	8 (22.90)	1
On Diuretics treatment	9 (25.70)	10 (28.60)	1
On Statins treatment	9 (25.70)	13 (37.10)	0.44
On Insulin	3 (8.60)	5 (14.30)	0.71
On Insulin +oral anti diabetic treatment	1(2.90)	2 (5.70)	1
On Oral anti diabetic treatment	4 (11.40)	2 (5.70)	0.673
Discharge medication, n (%)			
Aspirin	35 (100)	35 (100)	1
Clopidogrel	11 (31.40)	13 (37.10)	0.802
Ticagrelor	24 (68.60)	22 (62.90)	0.802
ACE inhibitors	26 (74.30)	28 (80.0)	0.777
ARBs	9 (25.70)	7 (20. 0)	0.777
Beta-blockers	30 (85.70)	31 (88.60)	1
Calcium-channel blocker	4 (11.40)	6 (17.10)	0.734
Statins	35 (100)	35 (100)	1
Nitrates	6 (17.10)	7 (20.0)	1
Diuretics	7 (20.0)	4 (11.4)	0.513
Aldosterone antagonists	10 (28.60)	7 (20.0)	0.578

Note: CoQ10 = of Coenzyme Q10; BMI=Body Mass Index; M/F = Male/Female; CK-MB: creatine kinease myocardial band isoenzyme; ACEI = Angiotensin-converting-enzyme inhibitors; ARB = angiotensin-receptor blocker; IQR= interquartile range (Q1–Q3).

femoral access site. The culprit's vessel was left anterior descending in the majority of patients (47.1%), followed by the right coronary artery (37.1%) and left circumflex (15.7%). The distribution of the culprit's vessel was similar in both groups. About 31.4% of patients had multivessel disease, and a high percentage of patients in both groups exhibited a TIMI flow grade or MBG 0-1 before PPCI. In nearly 17% of the patients, GP IIb/IIIa inhibitors were injected, and thrombus aspiration catheters were used in 12.9% of cases. All stents were everolimus-eluting stents.

Clinical efficacy outcomes

Results for the study endpoints are shown in Table 2 and Figures 2 and 3. As shown in Table 2, there were no significant differences between the study groups regarding TIMI flow grade and MBG at baseline. After completion of PPCI, no significant differences were found between the treatment groups in these parameters, as the mean value of TIMI flow grade and MBG were comparable between the two groups (TIMI flow grade: 2.83± 0.38 versus 2.74± 0.44; p-value= 0.390; MBG: 2.71± 0.52 versus 2.60± 0.60; p-value= 0.399). The analysis of the percentage of patients who met complete myocardial reperfusion at the end of PPCI, defined as TIMI flow grade 3 and MBG 3, also did not show a significant difference between the study groups (TIMI flow grade: 82.9% versus 74.3%; p-value= 0.561; MBG: 74.3% versus 65.7%; p-value= 0.688). Consistent

with these findings, there was also no between-group difference regarding the proportion of patients who achieved ECG criteria of successful myocardial reperfusion 60 minutes after the procedure, defined as ST-segment elevation resolution ≥70% (80.0% versus 71.4%; p-value= 0.665).

Results concerning the plasma levels of cardiac enzymes at different time points after PPCI have been shown in Figures 2a and 2b. The mean plasma levels of CK-MB and TnI before PPCI were similar between the treatment groups (p-value=0.539 and 0.392, respectively). This is while at 12, 24, 48, and 72 hours after PPCI, there was a significant difference between the treatment groups, as the mean plasma levels of CK-MB and TnI at all these time points were significantly lower in patients receiving CoQ10 compared to those receiving placebo (p-value < 0.010 for all time points).

In echocardiography, the CoQ10-supplemented patients exhibited better left ventricular function at 28 days follow-up compared to the control group (Table 2 and Figure 3). At baseline, the median (IQR) LVEF value and the proportion of patients with LVSD (defined as LVEF less than 50%) were comparable between the treatment groups (p-value = 0.448 and 0.303, respectively). On day 28, we noted a significant difference between the two groups, as the median (IQR) LVEF value was significantly higher in participants receiving CoQ10 relative to those receiving

Table 2. Comparison of study end points between two groups.

Variable	CoQ10 treated-Group (35 patients)	Placebo treated-Group (35 patients)	P-value
Angiographic outcomes			
TIMI flow grade pre-PCI, (mean±SD)	0.69± 0.83	0.71± 0.78	0.883
TIMI flow grade pre-PCI, n (%)			0.894
Grade 0	18 (51.4)	16 (45.7)	
Grade 1	11 (31.4)	14 (40.0)	
Grade 2	5 (14.3)	4 (11.4)	
Grade 3	1 (2.90)	1 (2.9)	
TIMI flow grade post-PCI, (mean±SD)	2.83± 0.38	2.74± 0.44	0.39
TIMI flow grade post-PCI, n (%)			0.561
Grade 2	6 (17.1)	9 (25.7)	
Grade 3	29 (82.9)	26 (74.3)	
MBG pre-PCI, (mean±SD)	0.51± 0.65	0.69± 0.83	0.343
MBG pre-PCI grade, n (%)			0.788
Grade 0	20 (57.1)	18 (51.4)	
Grade 1	12 (43.3)	11 (31.4)	
Grade 2	3 (8.6)	5 (14.3)	
Grade 3	0 (0.0)	1 (2.9)	
MBG post-PCI, (mean±SD)	2.71± 0.52	2.60± 0.60	0.399
MBG post-PCI grade, n (%)			0.688
Grade 1	1 (2.9)	2 (5.8)	
Grade 2	8 (22.9)	10 (28.6)	
Grade 3	26 (74.3)	23 (65.7)	
Electrocardiogram			
ST-segment resolution 60 min post-PCI, n (%)			0.665
Absent (<30%)	1 (2.9)	2 (5.8)	
Partial (30 to <70%)	6 (17.1)	8 (22.9)	
Complete (≥70%)	28 (80.0)	25 (71.4)	
Echocardiograph parameter			
LV ejection fraction at baseline (%)	53.00 (7.00)	52.00 (5.00	0.448
LV ejection fraction at day 28 (%)	52.00 (7.00)	50.00 (7.00)	0.034

CoQ10 = of Coenzyme Q10; TIMI = Thrombolysis In Myocardial Infarction; PCI = percutaneous coronary intervention; MBG = myocardial blush grade; IQR= interquartile range (Q1–Q3).

placebo (52.00 [7.00] versus 50.00 [7.00]; p-value= 0.034). Consistent with these results, there was a trend in a significant difference between the groups regarding the proportion of patients with LVSD (Figure 3), as the proportion of patients with LVED less than 50% was lower in patients receiving CoQ10 compared to those receiving placebo (37.10% versus 60.00%; p-value= 0.056).

Safety and Adverse events
In terms of safety, 18 adverse events were recorded in 12 cases receiving CoQ10 and 16 in 13 cases receiving placebo. The most commonly reported adverse effects were dyspepsia and nausea, which decreased by taking the medication with food. No serious adverse events were observed. Thus, no significant differences by study treatment were found in the frequency of patients reporting adverse effects.

Discussion
To the best of our knowledge, this is the first randomized controlled trial that specifically explored the potential therapeutic effects of CoQ10 supplementation on successful myocardial reperfusion, myocardial ischemia-reperfusion injury, and left ventricular function in patients with STEMI undergoing PPCI. Based on the study results, the rate of successful myocardial perfusion after completion of PPCI, assessed by TIMI flow grade, MBG, and ST-segment elevation resolution, did not differ in patients receiving CoQ10 compared to those receiving placebo. Nonetheless, patients supplemented with CoQ10 showed lower plasma levels of CK-MB and TnI at 12, 24, 48, and 72 hours after the procedure and exhibited better left ventricular function at 28 days follow-up, as LVEF less than 50% was less frequent in patients receiving CoQ10
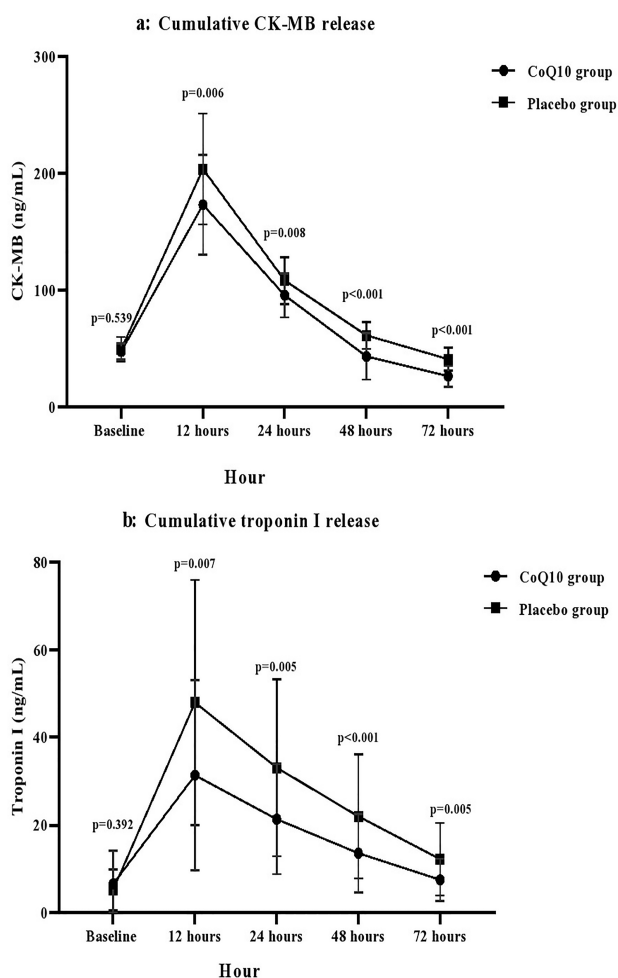
Figure 2. Time-concentration curve of (a) creatine kinease myocardial band isoenzyme (CK-MB) and (b) troponin I, showing mean and standard error. The p-values less than 0.010 based on Bonferroni's multiple testing correction method were considered statistically significant.
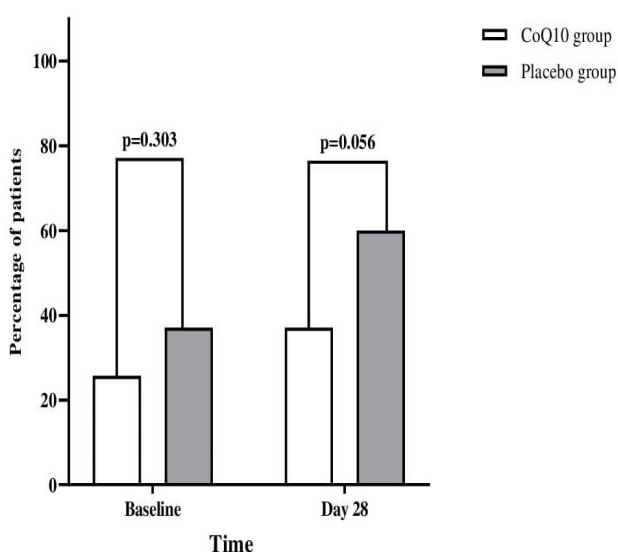
Figure 3. Comparison of the proportion of patients with left ventricular ejection fraction (LVEF) less than 50% at baseline and at day 28 between the study groups.

than those receiving placebo.

It is well known that the extent of myocardial damage and infarct size is the main determinant of left ventricular remodeling and dysfunction after acute myocardial infarction.[38,39] Therefore, any agent which can prevent myocardial damage during myocardial ischemia and reperfusion would be an important therapeutic aid to prevent complications after acute myocardial infarction. Research on animal models of ischemia-reperfusion injury has consistently supported that CoQ10 can exert a protective effect against ischemia-reperfusion injury, reduce myocardial infarct size, and improve cardiac function parameters.[27] Results of one study revealed that patients with STEMI who had higher plasma levels of CoQ10 at one month after PPCI exhibited better left ventricular function at a 6-month follow-up. This study also showed higher plasma levels of CoQ10 were associated with lower-grade oxidative stress and inflammatory status.[18] These findings suggest that CoQ10 supplementation by restoring its plasmatic and myocardial levels during myocardial ischemia and reperfusion can exert cardioprotective effects against ischemia-reperfusion injury. In the last years, a number of clinical studies have investigated this hypothesis. In this context, the results of a study conducted by Singh *et al.*[30] revealed that early administration of CoQ10 at a dose of 120 mg/d and continued for 28 days could significantly reduce total cardiac events such as angina pectoris, arrhythmias, and poor left ventricular function in patients with acute myocardial infarction during 28 days follow-up. This study also showed that compared to placebo, patients supplemented with CoQ10 had higher plasma levels of antioxidants, such as vitamins A, E, and C, and beta-carotene and lower levels of oxidative stress indicators, such as lipid peroxides, diene conjugates, and malondialdehyde.Compared to our study, they used a lower dose of CoQ10 which indicates CoQ10, even at a lower dose, can exert its cardioprotective effects against myocardial ischemia injury and improve cardiac outcomes after acute myocardial infarction. Results of another study conducted by this author and team showed that early administration of CoQ10 at a dose of 120 mg/day after acute myocardial infarction to patients with left ventricular ejection fraction <50%, and continued it for 24 weeks was associated with a reduction of left ventricular remodeling in these patients. In this study, compared to the control group, patients supplemented with CoQ10 have a lower serum level of angiotensin-converting enzyme (ACE), suggesting the beneficial effects attributable to CoQ10 on left ventricular remodeling at least partly related to its ameliorative effects on ACE function .[31] Compared to our study, they used a lower dose of CoQ10 for a longer duration and included only patients who had left ventricular dysfunction before CoQ10 treatment. Thus, their results indicated that CoQ10 administered early after acute myocardial infarction might prevent left ventricular remodeling and dysfunction in patients with persistent left ventricular dysfunction. In contrast to these

studies, results of a small randomized clinical trial study in patients with acute myocardial infarction showed that treatment with CoQ10 (100 mg/d) plus selenium (100 mg/d) for one year did not have significant effects on the occurrence of ventricular arrhythmias, cardiac failure, and other clinical outcomes in the study patients, but it was associated with a lower cardiac-related death during the one-year follow-up.[40] It seems that the relatively small number of participants might reduce the power of the study to detect a significant difference in the study endpoints between the groups. Results of another randomized clinical trial in patients with myocardial infarction demonstrated that CoQ10 supplementation at a dose of 200 mg/day for 12 weeks could reduce serum levels of inflammatory cytokines like interleukin-6 (IL-6) and intercellular adhesion molecules (ICAMs) that have essential roles in myocardial injury following acute myocardial infarction.[41] This study suggests that the cardioprotective effects of CoQ10 on acute myocardial infarction, at least partly, are mediated through its anti-inflammatory properties. The impact of CoQ10 supplementation on the quality of life of patients with myocardial infarction has also been investigated in one study. In this context, results of one study demonstrated that supplement therapy with CoQ10 (150 mg/d) and L-carnitine (200 mg/d) for three months could improve global, physical, and emotional well-being in patients with myocardial infarction assessed by the MacNew questionnaire. It seems that CoQ10, through improving post-myocardial infarction clinical outcomes, such as heart function, may improve the quality of life of these patients.[42] The cardioprotective effects of CoQ10 in elective percutaneous coronary intervention (PCI) have been also investigated. Results of one double-blinded randomized clinical trial in patients scheduled for elective PCI showed that 300 mg loading dose CoQ10 administrated 12 hours before the procedure did not have significant effects on plasma levels of CK-MB and TnI, but it significantly reduced plasma levels of high-sensitivity C-reactive protein (hs-CRP).[43] The authors concluded that a longer duration of treatment might be needed to observe the cardioprotective effects of CoQ10 against reperfusion injury.

Some clinical studies have also focused on the potential cardioprotective effect of supplementary CoQ10 on the clinical outcomes of patients undergoing CABG surgery. A recent meta-analysis of four clinical trials conducted in this setting demonstrated that preoperative treatment of CoQ10 could improve clinical outcomes of patients undergoing CABG by decreasing reperfusion arrhythmias and inotropic requirements; however, according to the results of this meta-analysis, CoQ10 had no significant impact on cardiac enzymes levels post-CABG.[28] Nonetheless, there are some other clinical studies demonstrating preoperative CoQ10 therapy could reduce cardiac enzyme levels in patients undergoing CABG.[44-46] The heterogeneity in the populations, the number of grafts, graft type, length of surgery, as well as doses and duration of CoQ10 therapy

might be potential reasons that partly explain these discrepant results. Since achieving the therapeutic plasma levels is very important in the effectiveness of antioxidant and anti-inflammatory agents, dosages of CoQ10 and duration of treatment seem to have an important impact on surrogate endpoints. In fact, a larger dose and a longer duration of treatment with CoQ10 should be used to achieve its therapeutic plasma level and observe its therapeutic effects.[47,48] Recently, the neuroprotective effects of CoQ10 against ischemia-reperfusion injury in acute ischemic stroke have been also investigated in one randomized clinical trial.[49] This study showed that administration of CoQ10 at a dose of 300 mg/day for four weeks in patients with acute ischemic stroke could improve neurological and cognitive impairments associated with stroke; however, CoQ10 did not have a significant effect on oxidative stress or neuro-inflammatory biomarkers. The authors suggested higher doses and a longer duration of treatment are needed to observe the inhibitory effects of CoQ10 on oxidative stress and inflammatory responses.[49] Our results extend these findings by showing that CoQ10 therapy may also be useful in STEMI patients by preventing myocardial ischemia-reperfusion injury and improving left ventricular function. Therefore, in light of this evidence, although a definitive conclusion regarding the therapeutic role of CoQ10 in conditions associated with ischemia-reperfusion injury is still inconclusive, the available evidence is encouraging.

Several potential mechanisms of action have been proposed to explain the cardioprotective effects of CoQ10 during myocardial ischemia-reperfusion injury.[49] It has been shown that CoQ10 can improve myocardial recovery and function by increasing cellular ATP synthesis.[50] Additionally, CoQ10 acts as a powerful antioxidant in the mitochondrial membrane and other subcellular fractions,[51] and can protect cell structures from oxidative damage during ischemia-reperfusion injury.[33,52] It is well documented that CoQ10 also acts as a potent anti-inflammatory agent and inhibits inflammatory responses. It is found that the anti-inflammatory action of CoQ10 is also mediated via its antioxidant effects.[53] Supporting this concept, a recent systematic review and meta-analysis of related randomized controlled trials found that CoQ10 supplementation could inhibit inflammatory and oxidative damage in patients with coronary artery disease.[54] The inhibitory effects of CoQ10 on inflammatory responses during elective PCI and acute myocardial infarction have also been reported in some clinical studies.[29,43] In addition to the above mechanisms, recent research has identified that CoQ10 has the ability to limit apoptotic myocardial cell death and reduce myocardial infarct size by regulating the expression and activity of pro- and anti-apoptotic proteins.[26,55] Some evidence indicates that CoQ10 may also have a regulatory effect on the renin-angiotensin-aldosterone system function, and reduce cardiac remodeling following myocardial infarction.[31] Additionally, it is thought that the ability of CoQ10 to

increase nitric oxide may result in coronary vasodilatation during myocardial ischemia.[55] Promising effects of CoQ10 supplementation on lipid profile,[56] blood pressure,[57] and platelet hyperactivity and aggregation[58] may be other mechanisms that can be beneficial in improving clinical outcomes following acute myocardial infarction.

One of the important properties of CoQ10 that introduces it as a potential candidate in the prevention and treatment of cardiovascular diseases is its safety and tolerability.[59] Clinical and preclinical data indicate that CoQ10 supplementation is highly safe and well tolerated and does not induce serious adverse effects in humans, even at high doses such as 2,400 mg/day.[60] Thus, in view of its mechanisms of action and excellent safety and tolerability, CoQ10 could be considered a suitable nutritional supplement in patients under ischemia-reperfusion conditions. However, further clinical studies are required to confirm the therapeutic role of CoQ10 in the prophylaxis and management of such patients.

Limitations and strengths of the study
This study has some limitations. The major limitation is that the number of patients enrolled is relatively small. However, despite this limitation, the study sample size seems to be sufficient to detect the significant effects of CoQ10 treatment on plasma levels of cardiac enzymes and left ventricular function in the study patients. Further, considering the single-centered nature of the study and the frequency of inclusion and exclusion criteria, the enrolled patients were a highly selected group of patients with STEMI scheduled for PPCI. This may limit the generalizability of our study results. Additionally, the study follow-up period was limited to 28 days; so we did not know the effects of CoQ10 supplementation on long-term outcomes in these patients. Further, we used a modest and consistent dose of CoQ10 in this study. Different doses of CQ10 may be associated with different efficacy and tolerability. Last but not least, due to the limitations of research grants, we did not assess the change in the plasma level of CoQ10 and the potential mechanisms of CoQ10 that, through them, may exert its beneficial effects in STEMI patients undergoing PPCI. Despite these limitations, our study has some strength. Our study is the first randomized controlled trial specifically exploring the cardioprotective effects of adjuvant CoQ10 supplementation in patients with STEMI undergoing PPCI. Further, we performed the statistics based on the ITT analysis which tends to be more conservative in estimating the treatment effect.

Conclusion
In summary, the results of the present study showed that 400 mg loading dose CoQ10 before the procedure in STEMI patients undergoing PPCI does not have a significant effect on successful myocardial perfusion after the procedure, assessed by TIMI flow grade, MBG, and ST-segment elevation resolution. It seems that the duration of CoQ10 therapy before the procedure was too short to have a significant effect on myocardial perfusion. Nevertheless, Nevertheless, continuing the CoQ10 supplementation with a dose of 200 mg twice a day in these patients might limit myocardial ischemia-reperfusion injury and might result in better left ventricular function in the short-term follow-up. However, given the limitations of this study, higher-quality randomized controlled studies with long-term follow-up are needed to better determine the potential therapeutic role of CoQ10 supplementation on long-term clinical outcomes and its possible mechanism actions in patients with acute myocardial infarction undergoing PPCI.

Ethics Issues
The trial protocol was conducted in line with the 2013 Helsinki Declaration, and the study protocol was approved by the research and ethics committee at Hamadan University of Medical Sciences (IR.UMSHA. REC.1400.623). The participants provided their written informed consent to participate in this study.

Data Sharing
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions
Amirhossein Yazdi: Investigation. Kimia Shirmohammadi: Investigation, Writing - Original Draft. Erfan Parvaneh: Investigation. Seyed Kianoosh Hosseini: Investigation. Akram Ranjbar: Methodology, Formal Analysis. Maryam Mehrpooya: Conceptualization, Methodology, Formal Analysis, Writing - Review & Editing.

Conflict of Interest
The authors report no conflicts of interest.

References
1. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. Am J Med. 2011;124(1):40-7. doi:10.1016/j.amjmed.2010.07.023
2. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet. 2017;389(10065):197-210. doi:10.1016/S0140-6736(16)30677-8
3. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007;357(11):1121-35.

doi:10.1056/NEJMra071667

4. Li X, Liu M, Sun R, Zeng Y, Chen S, Zhang P. Protective approaches against myocardial ischemia reperfusion injury. Exp Ther Med. 2016;12(6):3823-9. doi:10.3892/etm.2016.3877

5. Wang Q-D, Pernow J, Sjöquist P-O, Rydén L. Pharmacological possibilities for protection against myocardial reperfusion injury. Cardiovasc Res. 2002;55(1):25-37. doi:10.1016/s0008-6363(02)00261-4

6. He J, Liu D, Zhao L, Zhou D, Rong J, Zhang L, et al. Myocardial ischemia/reperfusion injury: Mechanisms of injury and implications for management. Exp Ther Med. 2022;23(6):430. doi:10.3892/etm.2022.11357

7. González-Montero J, Brito R, Gajardo AI, Rodrigo R. Myocardial reperfusion injury and oxidative stress: Therapeutic opportunities. World J Cardiol. 2018;10(9):74. doi:10.4330/wjc.v10.i9.74

8. Algoet M, Janssens S, Himmelreich U, Gsell W, Pusovnik M, Van den Eynde J, et al. Myocardial ischemia-reperfusion injury and the influence of inflammation. Trends Cardiovasc Med. 2022. doi:10.1016/j.tcm.2022.02.005

9. Ong S-B, Hernández-Reséndiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek X-Y, Cabrera-Fuentes HA, et al. Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities. Pharmacol Ther. 2018;186:73-87. doi:10.1016/j.pharmthera.2018.01.001

10. Brookes PS, Yoon Y, Robotham JL, Anders M, Sheu S-S. Calcium, ATP, and ROS: a mitochondrial love-hate triangle. Am J Physiol Cell Physiol. 2004;287(4):C817-33. doi: 10.1152/ajpcell.00139.2004

11. Seropian IM, Toldo S, Van Tassell BW, Abbate A. Anti-inflammatory strategies for ventricular remodeling following ST-segment elevation acute myocardial infarction. J Am Coll Cardiol. 2014;63(16):1593-603. doi: 10.1016/j.jacc.2014.01.014

12. Chen J, Chow S. Antioxidants and myocardial ischemia: reperfusion injuries. Chang Gung Med J. 2005;28(6):369-77.

13. Shinde S, Patil N, Tendolkar A. Coenzyme Q10: A review of essential functions. Internet J Nutr Wellness. 2005;1(2):1-19.

14. Belardinelli R, Tiano L, Littarru GP. Oxidative stress, endothelial function and coenzyme Q_ {10}. Biofactors. 2008;32(1-4):129-33. doi:10.1002/biof.5520320115

15. Fan L, Feng Y, Chen G-C, Qin L-Q, Fu C-l, Chen L-H. Effects of coenzyme Q10 supplementation on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Pharmacol Res. 2017;119:128-36. doi:10.1016/j.phrs.2017.01.032.

16. Bogeski I, Gulaboski R, Kappl R, Mirceski V, Stefova M, Petreska J, et al. Calcium binding and transport by coenzyme Q. J Am Chem Soc. 2011;133:9293-303. doi:10.1021/ja110190t.

17. Gutierrez-Mariscal FM, Yubero-Serrano EM, Villalba JM, Lopez-Miranda J. Coenzyme Q10: From bench to clinic in aging diseases, a translational review. Crit Rev Food Sci Nutr. 2019;59(14):2240-57. doi:10.1080/10408398.2018.1442316

18. Huang C-H, Kuo C-L, Huang C-S, Tseng W-M, Lian IB, Chang C-C, et al. High plasma coenzyme Q10 concentration is correlated with good left ventricular performance after primary angioplasty in patients with acute myocardial infarction. Medicine (Baltimore). 2016;95(31):e4501. doi:10.1097/MD.0000000000004501

19. Shimizu M, Miyazaki T, Takagi A, Sugita Y, Yatsu S, Murata A, et al. Low circulating coenzyme Q10 during acute phase is associated with inflammation, malnutrition, and in-hospital mortality in patients admitted to the coronary care unit. Heart Vessels. 2017;32(6):668-73. doi:10.1007/s00380-016-0923-x

20. Shimizu M, Miyazaki T, Takagi A, Sugita Y, Ouchi S, Aikawa T, et al. Low coenzyme Q10 levels in patients with acute cardiovascular disease are associated with long-term mortality. Heart Vessels. 2021;36(3):401-7. doi:10.1007/s00380-020-01698-7

21. Pepe S, Marasco SF, Haas SJ, Sheeran FL, Krum H, Rosenfeldt FL. Coenzyme Q10 in cardiovascular disease. Mitochondrion. 2007;7:S154-67. doi:10.1016/j.mito.2007.02.005.

22. Gaby AR. The role of coenzyme Q10 in clinical medicine: Part II. Cardiovascular disease, hypertension, diabetes mellitus, and infertility. Altern Med Rev. 1996;1(3):168-75.

23. Sugawara H, Yamamoto T, Shimizu S, Momose K. Inhibition of ubiquinone synthesis in isolated rat heart under an ischemic condition. Int J Biochem. 1990;22(5):477-80. doi:10.1016/0020-711x(90)90260-a.

24. Judy W, Stogsdill W, Folkers K. Myocardial preservation by therapy with coenzyme Q 10 during heart surgery. Clin Investig. 1993;71(8 Suppl):S155-61. doi:10.1007/BF00226859.

25. Muscari C, Magnani B, Biagette L, Stefanelli C, Capucci A, Caldarera C. Protective effects of coenzyme Q10 administration and relationship with its reduced biosynthesis in the ischemic and reperfused myocardium. Biomedical and clinical aspects of coenzyme Q10. Amsterdam: Elsevier;1991. p. 301-10.

26. Liang S, Ping Z, Ge J. Coenzyme Q10 regulates antioxidative stress and autophagy in acute myocardial ischemia-reperfusion injury. Oxid Med Cell Longev. 2017;2017:9863181. doi:10.1155/2017/9863181

27. Awad K, Sayed A, Banach M. Coenzyme Q10 Reduces Infarct Size in Animal Models of Myocardial Ischemia-Reperfusion Injury: A Meta-Analysis and Summary of Underlying Mechanisms. Front Cardiovasc Med. 2022;9:857364. doi:10.3389/fcvm.2022.857364

28. Bulatao DP, Banez C. Effect of preoperative treatment of oral coenzyme q10 on reperfusion arrhythmias and myocardial protection in patients undergoing coronary artery bypass graft (CABG). J Arrhythm. 2011;27(4):433. doi:10.4020/jhrs.27.pe4_020

29. Hadi NR, Amber KI, Aziz ND. Acute inflammatory response after novolimus drug eluting stent implantation in diabetic patients with coronary artery disease and the impact of coenzyme Q10. World Heart J. 2018;10(1):33-43.

30. Singh RB, Wander GS, Rastogi A, Shukla PK, Mittal A, Sharma JP, et al. Randomized, double-blind placebo-controlled trial of coenzyme Q10 in patients with acute myocardial infarction. Cardiovasc Drugs Ther. 1998;12(4):347-53. doi:10.1023/a:1007764616025

31. Singh RB, Fedacko J, Mojto V, Pella D. Coenzyme Q10 modulates remodeling possibly by decreasing angiotensin-converting enzyme in patients with acute coronary syndrome. Antioxidants (Basel). 2018;7(8):99. doi:10.3390/antiox7080099

32. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-177. doi:10.1093/eurheartj/ehx393

33. Beyer RE. An analysis of the role of coenzyme Q in free radical generation and as an antioxidant. Biochem Cell Biol. 1992;70(6):390-403. doi:10.1139/o92-061

34. Chesebro J, Knatterud G, Roberts R, Borer J, Cohen L, Dalen J, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation. 1987;76(1):142-54. doi:10.1161/01.cir.76.1.142

35. van 't Hof AWJ, Liem A, Suryapranata H, Hoorntje JC, de Boer M-J, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation. 1998;97(23):2302-6. doi:10.1161/01.cir.97.23.2302

36. Schröder R, Dissmann R, Brüggemann T, Wegscheider K, Linderer T, Tebbe U, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol. 1994;24(2):384-91. doi:10.1016/0735-1097(94)90292-5

37. Basili S, Tanzilli G, Mangieri E, Raparelli V, Di Santo S, Pignatelli P, et al. Intravenous ascorbic acid infusion improves myocardial perfusion grade during elective percutaneous coronary intervention: relationship with oxidative stress markers. JACC Cardiovasc Interv. 2010;3(2):221-9. doi:10.1016/j.jcin.2009.10.025

38. Frank A, Bonney M, Bonney S, Weitzel L, Koeppen M, Eckle T. Myocardial ischemia reperfusion injury: from basic science to clinical bedside. Semin Cardiothorac Vasc Anesth. 2012;16(3):123-32. doi:10.1177/1089253211436350

39. Neri M, Riezzo I, Pascale N, Pomara C, Turillazzi E. Ischemia/reperfusion injury following acute myocardial infarction: a critical issue for clinicians and forensic pathologists. Mediators Inflamm. 2017;2017:7018393. doi:10.1155/2017/7018393

40. Kuklinski B, Weissenbacher E, Fähnrich A. Coenzyme Q10 and antioxidants in acute myocardial infarction. Mol Aspects Med. 1994;15:s143-7. doi:10.1016/0098-2997(94)90023-x

41. Mohseni M, Vafa M, Zarrati M, Shidfar F, Hajimiresmail SJ, Forushani AR. Beneficial effects of coenzyme Q10 supplementation on lipid profile and intereukin-6 and intercellular adhesion molecule-1 reduction, preliminary results of a double-blind trial in acute myocardial infarction. Int J Prev Med. 2015;6:73. doi:10.4103/2008-7802.162461

42. Sharifi MH, Eftekhari MH, Ostovan MA, Rezaianazadeh A. Effects of a therapeutic lifestyle change diet and supplementation with Q10 plus L-carnitine on quality of life in patients with myocardial infarction: a randomized clinical trial. J Cardiovasc Thorac Res. 2017;9(1):21-8. doi:10.15171/jcvtr.2017.03

43. Aslanabadi N, Safaie N, Asgharzadeh Y, Houshmand F, Ghaffari S, Garjani A, et al. The randomized clinical trial of coenzyme Q10 for the prevention of periprocedural myocardial injury following elective percutaneous coronary intervention. Cardiovasc Ther. 2016;34(4):254-60. doi:10.1111/1755-5922.12195

44. Makhija N, Sendasgupta C, Kiran U, Lakshmy R, Hote MP, Choudhary SK, et al. The role of oral coenzyme Q10 in patients undergoing coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth. 2008;22(6):832-9. doi:10.1053/j.jvca.2008.03.007

45. Sunamori M, Tanaka H, Maruyama T, Sultan I, Sakamoto T, Suzuki A. Clinical experience of coenzyme Q10 to enhance intraoperative myocardial protection in coronary artery revascularization. Cardiovasc Drugs Ther. 1991;5(Suppl 2):297-300. doi:10.1007/BF00054751

46. Moludi J, Keshavarz S, Tabaee AS, Safiri S, Pakzad R. Q10 supplementation effects on cardiac enzyme CK-MB and troponin in patients undergoing coronary artery bypass graft: a randomized, double-blinded, placebo-controlled clinical trial. J Cardiovasc Thorac Res. 2016;8(1):1-7. doi:10.15171/jcvtr.2016.01

47. Martelli A, Testai L, Colletti A, Cicero AF. Coenzyme Q10: Clinical applications in cardiovascular diseases. Antioxidants (Basel). 2020;9(4):341. doi:10.3390/antiox9040341

48. Sue-Ling CB, Abel WM, Sue-Ling K. Coenzyme Q10 as adjunctive therapy for cardiovascular disease and hypertension: A systematic review. J Nutr. 2022;152(7):1666-74. doi:10.1093/jn/nxac079

49. Ramezani M, Sahraei Z, Simani L, Heydari K, Shahidi F. Coenzyme Q10 supplementation in acute ischemic stroke: Is it beneficial in short-term administration? Nutr Neurosci. 2020;23(8):640-5. doi:10.1080/1028415X.2018.1541269

50. Crestanello JA, Kamelgard J, Lingle DM, Mortensen SA, Rhode M, Whitman GJ. Elucidation of a tripartite mechanism underlying the improvement in cardiac tolerance to ischemia by coenzyme Q10 pretreatment. JTCVS Open. 1996;111(2):443-50. doi:10.1016/S0022-5223(96)70455-5

51. Forsmark-Andree P, Ernster L. Evidence for a protective effect of endogenous ubiquinol against oxidative damage to mitochondrial protein and DNA during lipid peroxidation. Mol Aspects Med. 1994;15:s73-81. doi:10.1016/0098-2997(94)90015-9

52. Akbari A, Mobini GR, Agah S, Morvaridzadeh M, Omidi A, Potter E, et al. Coenzyme Q10 supplementation and oxidative stress parameters: a systematic review and meta-analysis of clinical trials. Eur J Clin Pharmacol. 2020;76(11):1483-99. doi:10.1007/s00228-020-02919-8

53. Ebadi M, Sharma S, Wanpen S, Amornpan A. Coenzyme Q10 inhibits mitochondrial complex-1 down-regulation and nuclear factor-kappa B activation. J Cell Mol Med. 2004;8(2):213-22. doi:10.1111/j.1582-4934.2004.tb00276.x

54. lami M, Heydari ST, et al. The effects of coenzyme Q10 supplementation on biomarkers of inflammation and oxidative stress in among coronary artery disease: a systematic review and meta-analysis of randomized controlled trials. Inflammopharmacology. 2019;27(2):233-48. doi:10.1007/s10787-019-00572-x

55. Khan NA, Abid M, Ahmad A, Abuzinadah MF, Basheikh M, Kishore K. Cardioprotective effect of coenzyme Q10 on apoptotic myocardial cell death by regulation of bcl-2 gene expression. J Pharmacol Pharmacother. 2017; 8(3):122-7. doi:10.4103/jpp.JPP_47_17

56. Jorat MV, Tabrizi R, Mirhosseini N, Lankarani KB, Akbari M, Heydari ST, et al. The effects of coenzyme Q10 supplementation on lipid profiles among patients with coronary artery disease: A systematic review and meta-analysis of randomized controlled trials. Lipids Health Dis. 2018;17(1):230. doi:10.1186/s12944-018-0876-4

57. Rosenfeldt FL, Haas SJ, Krum H, Hadj A, Ng K, Leong JY, et al. Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. J Hum Hypertens. 2007;21(4):297-306. doi:10.1038/sj.jhh.1002138

58. Wang R, Chen Y, Tian Z, Zhu M, Zhang B, Du S, et al. Coenzyme Q10 Attenuates Human Platelet Aggregation Induced by SARS-CoV-2 Spike Protein via Reducing Oxidative Stress In Vitro. Int J Mol Sci. 2022;23(20):12345. doi:10.3390/ijms232012345

59. Arenas-Jal M, Suñé-Negre J, García-Montoya E. Coenzyme Q10 supplementation: Efficacy, safety, and formulation challenges. Compr Rev Food Sci Food Saf. 2020;19(2):574-94. doi:10.1111/1541-4337.12539

60. Zhu Z-G, Sun M-X, Zhang W-L, Wang W-W, Jin Y-M, Xie C-L. The efficacy and safety of coenzyme Q10 in Parkinson's disease: a meta-analysis of randomized controlled trials. Neurol Sci. 2017;38(2):215-24. doi:10.1007/s10072-016-2757-9