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ORIGINAL ARTICLE

Impact of quercetin in patients with myocardial infarction. A multicenter, randomized, and open-label pilot study

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ABSTRACT

OBJECTIVE Myocardial infarction (MI) is one of the leading causes of death in the world. Early myocardial reperfusion improves acute MI survival. Bioflavonoid quercetin is known to have antioxidant, anti-inflammatory, and anti-proliferative properties. The presented pilot study aims to investigate the cardioprotective effect of quercetin on infarct size limiting in patients with ST-segment elevation myocardial infarction (STEMI).

METHODS Patients (n = 143) with first anterior STEMI within 6 hours from symptoms onset were included in this open-label multicenter pilot study. Patients were randomized either into quercetin group (n = 70) in addition to standard treatment or recommended therapy alone group (control group, n = 73). Quercetin infusions were initiated before reperfusion and repeated during the next 5 days. The infarct size assessed using creatine kinase-myocardial band area under curve (CK-MB AUC) was the primary study outcome.

RESULTS The study arms did not differ in demographics, time to admission, and main clinical data. The median early CK-MB AUC was significantly lower in quercetin group than in controls (8036 ± 7594 vs 11219 ± 8146 U × 1 h/L, p = 0.015). Intravenous quercetin administration was associated with less reperfusion-induced intramyocardial hemorrhage by Cardiac Magnetic Resonance on Day 3 (11.1% of patients in quercetin group vs 53.3% of patients in control group, p < 0.024). There were no significant differences in left ventricle ejection fraction and LV remodeling indicators.

CONCLUSION Our pilot study is the first to demonstrate novel insight into ischemia/reperfusion damage in STEMI patients. The addition of quercetin to standard STEMI therapy limits infarct size and prevents intramyocardial hemorrhage after the first anterior STEMI. Further research will be necessary to both validate and expand upon these findings. (Hellenic Journal of Cardiology 2024;76:68-74) © 2023 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. INTRODUCTION

Cardiomyocyte viability directly depends on the duration of coronary artery (CA) obstruction; the longer the occlusion time, the greater the myocardial damage. Hence, the theory of open CA and the "golden hour" during which a part of the myocardium can be saved is crucial in the myocardial infarction (MI) prognosis. It is well established that early reperfusion of the infarct-related CA is essential for the preservation of myocardial tissue and it optimizes outcomes in patients with ST-elevation MI (STEMI)[1].

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However, this approach is complicated by ischemia/reperfusion injury, ventricular arrhythmias, myocardial stunning, and micro-vascular obstruction in addition to cardiomyocyte death[2]. The most important factors contributing to reperfusion injury are reactive oxygen species, intracellular calcium overload, mitochondrial injury, and inflammation. Experimental animal studies applied various medications and mostly demonstrated limitations of infarct size. A series of experimental data also confirmed that quercetin has significant anti-inflammatory, antioxidant, and anti-apoptotic effects in animal acute myocardial infarction (AMI) models, and can effectively protect against myocardium damage[3,4]. However, this has not yet been translated into real clinical practice. Nevertheless, the search for new cardioprotective drugs is critical and still ongoing[5,6]. Among the landmark clinical studies, the large randomized European Myocardial Infarction Project-Free Radicals trimetazidine trial failed potentially due to poor study design, low quality, and patient retention[7]. Further cardioprotective strategies include cyclosporine A, exenatide, adenosine, glucose-insulin-potassium, nitric oxide signaling, modulating mitochondria, atrial natriuretic peptide, and applying other agents, such as losmapimod, FX06, IK-5001, etc., and regenerative agents[6,8]. However, none of these drugs have been used in clinical practice.

Quercetin or pentaoxyflavone is an aglycon of flavonoid glycoside rutin that affects the activity of enzymes involved in the degradation of phospholipids (phospholipase, lipoxygenase, cyclooxygenase), modulating free radical formation, nitric oxide production, and metabolism[9]. Quercetin is known to have anti-inflammatory, anti-coagulative, and anti-proliferative properties. Since quercetin is difficult to dissolve in water, the intravenous formulation has been developed using nanotechnology by adsorbing drug molecules onto a special carrier of 50-100 microns in size.

The objective of this study was to examine whether quercetin reduces infarct size with standard therapy compared to standard therapy alone in patients with reperfused STEMI.

2. MATERIAL AND METHODS

2.1. STUDY DESIGN AND POPULATION. This multicenter randomized clinical trial of the efficacy and safety of intravenous quercetin enrolled 143 patients with STEMI from 15 centers. 73 patients were assigned to the placebo group, and 70 patients were treated with quercetin. The trial was approved by the institutional review boards and ethics committees. Patients who met the following criteria and gave written informed consent were eligible for randomization: 18 to 85 years of age; first anterior STEMI documented according to standard criteria; hospitalization within 6 hours from the onset of the symptoms; indications for reperfusion therapy. Patients with previous MI, cardiogenic shock, atrial fibrillation, New York Heart Association class III-IV heart failure, severe renal and liver failure, uncontrolled type 1 or 2 diabetes mellitus, cancer, participation in another clinical study in the last 3 months, and previous or current abuse of drugs or alcohol were excluded. The detailed design and criteria were published in a previous publication[9]. Patients were randomly assigned in a 1:1 ratio to quercetin or standard care groups. Quercetin (Corvitin®, BCPP, Ukraine) infusions were started before reperfusion and repeated during the next 5 days. Quercetin continuous intravenous infusion (500 mg of quercetin and 50 ml 0.9% Sodium Chloride) for 15-20 minutes: Day 1-first injection after hospitalization, the second injection after 2 hours and the third injection 12 hours after the previous injection; Days 2 and 3-2 times a day with an interval of 12 hours; Days 4 and 5-once a day.

Transthoracic echocardiography (TTE) was performed in all patients after hospitalization, before mechanical or pharmacological reperfusion therapy, on Days 10 and 90.

This study consists of two sub-studies conducted on one site:

1. STEMI patients (n = 37) were randomized to undergo speckle tracking imaging (global longitudinal strain (GLS), global radial strain (GRS), and global circumferential strain (GCS)) on days 1, 10, and 90. Eighteen patients were randomized into the quercetin group and 19 patients into the control group.
2. An additional group of STEMI patients (n = 23) was recruited to assess LV edema with evaluation of microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH) using ECG-gated Cardiac Magnetic Resonance (CMR) within the first week (3.5 ± 1.2 days) after STEMI. Nine patients were randomized into quercetin group and fourteen patients into the control group. Area at risk (AAR) was detected in late gadolinium enhancement images indicating MI. MVO was determined as a persisting area of hypoenhancement within regions of early gadolinium enhancement (EGE), and IMH was detected by using T2

ABBREVIATIONS

MI = myocardial infarction

STEMI = ST-segment elevation myocardial infarction

LVEF = left ventricle ejection fraction

CA = coronary artery

GLS = global longitudinal strain

GRS = global radial strain

GCS = global circumferential strain

MVO = microvascular obstruction

IMH = intramyocardial hemorrhage

CMR = cardiac magnetic resonance

TABLE 1 Baseline clinical characteristics and medications of the STEMI patients

	Study group (n = 70)	Control group (n = 73)
Age, years	57.7 ± 9.1	57.3 ± 9.2
Male, %	86.1	87.3
BMI, kg/m^2	27.4 ± 4.4	28.4 ± 4.6
Reperfusion, %	97.1	98.6
EDI, ml/m^2	60,9 ± 7,1	65,2 ± 9,3
ESI, ml/m^2	29,9 ± 4,9	33,2 ± 6,8
LV EF, %	51.1 ± 7.7	48.9 ± 7.5
LA, mm	37,0 ± 3,0	37,5 ± 2,7
IVSd, mm	11,1 ± 3,0	10,9 ± 3,3
PWd, mm	10,4 ± 2,3	10,3 ± 3,1
E/A, y.e.	1,0 ± 0,4	1,1 ± 0,3
E/e'.	6,7 ± 1,5	6,9 ± 2,0
DT, ms	184,9 ± 44,4	184,1 ± 40,5
IVRT, ms	102,4 ± 20,4	103,8 ± 16,2
HR, bpm	75,6 ± 13,5	74,4 ± 13,2
CI, l/min/m^2	2,0 ± 0,4	2,1 ± 0,5
Time from symptoms onset, h	2.96	2.97
Arterial hypertension, %	51.4	65.8
Diabetes mellitus, %	5.7	9.6
Smoking, %	50.0	52.1
Angina pectoris, %	10.0	16.4
History of MI, %	0	0
Stroke, %	0	0
ACE/ARBs, %	79.7/1.4	84.9/0
Beta blockers, %	92.9	84.9
Aspirin, %	97.1	93.2
Ticagrelor, %	67.1	52.1
MRAs, %	40.6	52.8
LMW heparins, %	95.7	97.3
Statins, %	94.3	93.2

No statistical differences between groups. *Abbreviations:* STEMI, ST-segment elevation myocardial infarction; IBM, index body mass; PTCA, percutaneous transluminal coronary angioplasty; TLT, thrombolytic therapy; EDI, end-diastole index; ESI, end-systole index; LA, left atrium; IVSd, interventricular septum thickness at end-diastole; PW, Left ventricular posterior wall thickness at end-diastole; DT, deceleration time; IVRT, isovolumic relaxation time; HR, heart rate; CI, cardiac index; LV EF, left ventricular ejection fraction; MI, myocardial infarction; ACE/ARBs, angiotensin-converting enzyme/angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; LMW heparin, low-molecular-weight heparin.

weighted imaging. In addition, infarct transmurality was graded visually into the following quarters indicating transmural damage, <25%, 25% to 50%, 51% to 75%, and 76% to 100%. All imaging data were blinded to investigators.

2.2. ENDPOINTS. The primary study endpoint was the infarct size index assessed using serial creatine kinase-myocardial band area under curve (CK-MB AUC). The secondary endpoints were, LV ejection fraction differences on Day 10 and Day 90 compared to those on Day 1; GLS, GRS, and GCS by speckle tracking imaging; AAR and IMH by CMR imaging with gadolinium enhancement.

2.3. STATISTICS. The target sample size of 150 patients was based on an assumption of a 20% reduction in the final infarct size associated with quercetin with a power of 80% at the alpha = 0.05 level. Data distribution was assessed using the Shapiro-Wilk test. Comparison between categorical variables was done using the chi-square test or Fischer's exact test, as appropriate. The Student t-test or Mann-Whitney U test were used for the comparison of continuous variables, as appropriate. The software SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses.

3. RESULTS

The study groups did not differ in demographic characteristics, time to admission from onset symptoms (median time 2.96 hours), reperfusion strategies (PCI 72%), and main clinical variables (Table 1).

Overall, quercetin reduced infarct size by 18% according to CK-MB AUC (Fig. 1). The median 48-h CK-MB AUC was significantly lower in quercetin group than in controls (8036 ± 7594 vs 11219 ± 8146 U × 1 h/L, $p < 0.015$).

TTE: Baseline LV EF was 51.90 ± 8.19% in quercetin group and 49.85 ± 7.75% in controls. There were no significant differences in LV EF (Fig. 2) between groups on Day 10 and after 3 Months.

Speckle-Tracking echocardiography revealed significant improvement of GLS in both groups on Day 7 and Day 90 of follow-up (Fig. 3).

However, patients in the quercetin group demonstrated a trend toward improvement of strain indicators in comparison to controls. In 3 months, GRS tended to increase in the quercetin group and decreased in controls, which may be attributed to the myocardial fibrosis after STEMI. Also, GCS tended to improve in the quercetin group during follow-up.

CMR imaging: CMR imaging was performed in 23 patients after a median of 3.5 days after STEMI (Table 1, Appendix 2) showing that the total number of all segments with edema was similar in both groups. However, the area at risk (infarct transmurality grade ≥50%) was significantly higher in quercetin group, 7.7 ± 1.2 compared to 6.2 ± 1.5 in controls ($p<0.027$) (Fig. 4).

Although AAR was initially greater in the study group compared to that in control group, quercetin demonstrated cardioprotective properties and significantly reduced infarct size.

MVO was detected in most patients according to early gadolinium-enhancement, 77.8% in quercetin group compared to 85.7% in controls ($p = 0.184$), though quercetin treatment was associated with a

significantly lower percentage of reperfusion-induced IMH on Day 3 after STEMI onset (11.1% of patients in quercetin group vs 53.3% of patients in control group, p = 0.024; Fig. 5).

3.1. ADVERSE EVENTS. Quercetin treatment was safe and well tolerated. The overall incidence of adverse events (laboratory abnormalities, rhythm disturbances, changes in blood pressure and heart rate, etc) was 12.6% in quercetin group and 18% in controls and that of serious adverse events was 10% in quercetin group and 12.3% in controls, without differences between the study groups. No serious adverse events were treatment-related that lead to death, interruption, or discontinuation of quercetin.

4. DISCUSSION

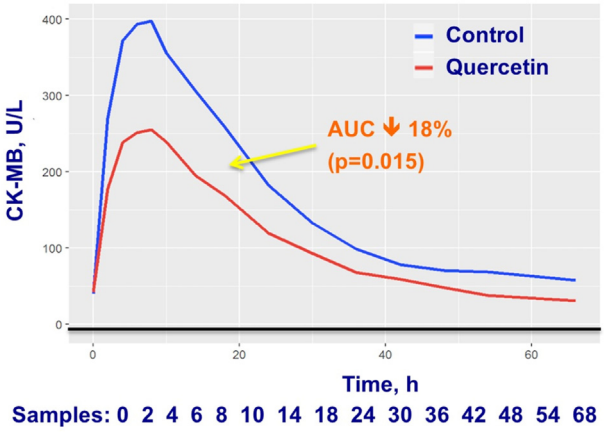
This randomized, open-label, multicenter pilot study is the first to demonstrate an 18% reduction of infarct size after the use of intravenous quercetin in patients presenting with an acute STEMI. Currently, there is no effective therapy to prevent MI-reperfusion injury and as imaging techniques show, it is present in many patients. Methods to effectively reduce infarct size have attracted the attention of medical researchers in recent years, but unfortunately, the experimental data have not been translated into real clinical practice.

Several small pilot clinical studies suggested that quercetin may improve nitric oxide and leukotriene metabolism, reducing oxidative stress and inflammation[10]. In fact, quercetin limits infarct size, reduces LV pathological remodeling, and increases myocardial contractility. Moreover, at long-term follow-up, quercetin reduced the incidence of cardiovascular death and non-fatal MI, but those studies were not randomized and single-centered[10,12].

Therefore, the results of the pilot study are of scientific significance, and further research is needed to find the selection of doses of the study drug and the duration of therapy.

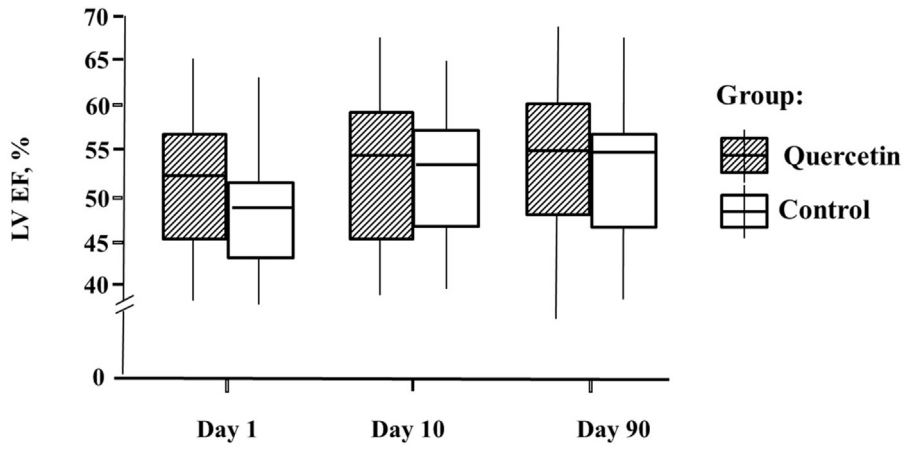
Improvement of ST-segment resolution at 3 hours after thrombolytic therapy was shown in patients with STEMI, pretreated with quercetin (65% vs, 47.5% in controls, p < 0.05)[13]. Another pilot study demonstrated that quercetin reduces infarct size in AMI patients following PCI (47.8 ± 3.4 vs 68.8 ± 5.1 g/eqv

FIGURE 1 Serial plasma CK-MB in 2 study arms over first 68 hours after index STEMI



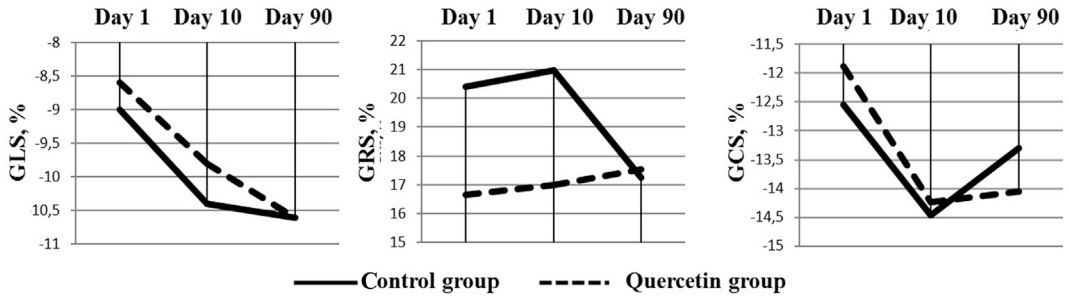
Samples were taken at 15 time points during the first 68 h. AUC – area under the curve; CK-MB – creatine kinase-MB fraction; h – hours.

FIGURE 2 Distribution of LV EF changes on admission, on Day 10 and Day 90 follow-up after STEMI. No statistically significant differences between groups were found in all terms



LVEF: Left ventricular ejection fraction.

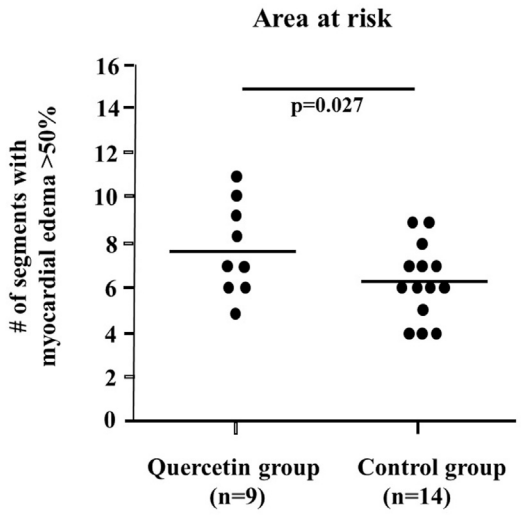
FIGURE 3 **The changes in Speckle-Tracking Imaging measurements (GLS, GRS, GCS) on admission, on Day 10, and Day 90 of follow-up after STEMI**



GLS - global longitudinal strain; GRS - global radial strain and GCS - global circumferential strain.

in control, $p < 0.05$)[14]. Analyses of myocardial salvage provide evidence to suggest that penetration of quercetin into the region of evolving infarction may have a beneficial effect by decreasing inflammation and stimulating vascular endothelial growth factor[15]; inhibiting lipoxygenase activity *in vivo* and causing a decrease in leukotriene C_4 and diene conjugates, and suppressing nitric oxide[11,15-17]. Also results of the FLAVOUR study demonstrate that 5-lipoxygenase-activating protein inhibitor AZD5718 provides robust inhibition of leukotriene biosynthesis via the 5-lipoxygenase pathway[18]. However, in another study, quercetin supplementation (500 mg/day) in post-MI patients for 8 weeks significantly elevated total antioxidant capacity and improved the insecurity dimension of quality of life, but failed to show any significant effect on inflammatory factors and blood pressure[19].

FIGURE 4 **Scatter dot plots for CMR measurement within the first week (3.5 ± 1.2 days) after STEMI. The area at risk - number of segments with myocardial edema >50% was 6.2 in the patients of the control group vs 7.7 in patients of quercetin group (p = 0.027). CMR-Cardiac Magnetic Resonance.**

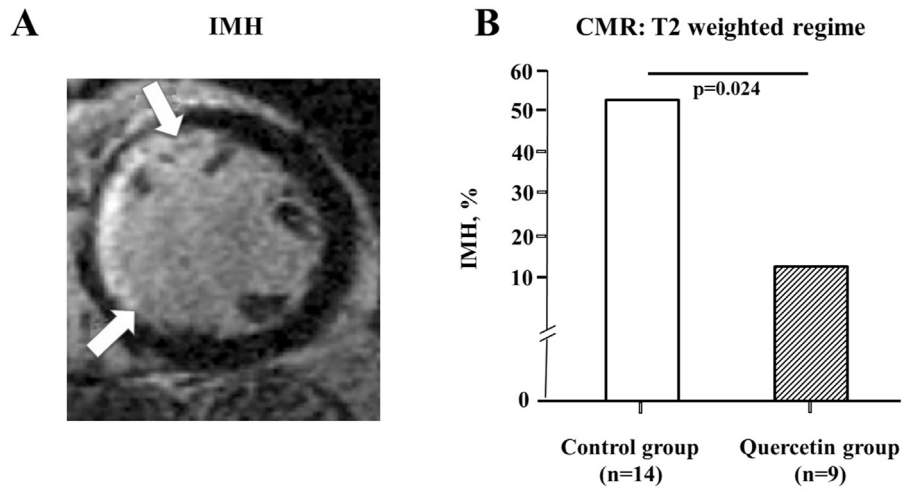


In AMI patients, quercetin improves renal function and reduces recurrent MI and cardiovascular death during 5 years of follow-up[12,20]. Importantly, initiation of quercetin infusion early at the time of admission, rather than after achieving complete reperfusion, may be beneficial. A recent review of adjunctive cardioprotection, concluded that the efficacy of such strategies appears to be optimal if initiated over the first 6 hours after the onset of ischemia[21].

The LV myocardium is composed of three layers. Myocardial damage extends from the endocardium and progresses as a wavefront to the epicardium. In our study, the improved GCS scores in the study groups are possibly associated with reduced damage of the mid-wall layer, with circumferentially oriented fibers, compared to that in the control group. However, our hypothesis needs to be confirmed. Our study demonstrated that MVO was detected in about 90% of patients of both groups according to LGE; however, IMH rate was higher in the control group than in the study group. A decrease in the rate of IMH despite high initial AAR in quercetin group possibly prevents the worsening of myocardial contractile function (by radial Strain). Both MVO and IMH have been recognized as poor prognostic factors in patients with AMI[22,23]. Another study suggests that quercetin may protect pial microcirculation from damage via arteriolar dilation likely by nitric oxide release[24].

Some evidence suggests that quercetin may favorably affect STEMI prognosis. In fact, a significant decrease in cardiovascular death, non-fatal MI, and unstable angina was observed over 6 years of follow-up[12]. However, the present study cannot establish causality, and further long-term analysis is required

FIGURE 5 **Cardiac Magnetic Resonance (CMR) Imaging: intramyocardial hemorrhage (IMH) (Day 3). A) CMR images from a patient with acute anterior myocardial infarction - Intramyocardial hemorrhage (yellow arrows)**



Attenuated T2W signal corresponding to hemorrhage in the infarct core. B) Number of patients with IMH in control group (54%) and quercetin group (11.1%) p = 0.024.

to determine whether only serial measurement of biomarkers meets the strict criteria to be considered a valid endpoint.

4.1. LIMITATIONS. This was a multicenter randomized, but open-label pilot study, with a small sample size and low statistical power. Use of CK-MB AUC method for infarct size measurement, differences in cardiac magnetic resonance imaging sub-study at baseline in the extent of myocardial ischemia area, and lack of long-term follow-up were the main study limitations.

5. CONCLUSION

Novel intravenous quercetin formula in patients with STEMI demonstrated possible cardioprotective properties: limitation of infarct size, IMH decrease, and GRS improvement, but failed to show any significant effect on LV EF, GLS, and GCS. However, further large multicenter clinical trials are needed to confirm our results and determine the impact of clinical outcomes improvement.

DECLARATIONS OF INTEREST

The authors have no conflicts of interest to declare.

STATEMENT OF ETHICS

All subjects have given their written informed consent.

This study protocol was reviewed and approved by Ethics Committee of the NSC "The M.D.Strazhesko Institute of Cardiology", approval number 1-49 dated 24.06.2014.

FUNDING

BCPP, Kyiv, Ukraine provided the drug for the study.

AUTHOR CONTRIBUTIONS

Sergey Kozhukhov: Conceptualization, Methodology, Writing - Review & Editing, Supervision. Alexander Parkhomenko: Writing - Review & Editing, Investigation. Yaroslav Lutay: Writing - Original Draft, Investigation. Nataliia Dovganych: Writing - Review and Editing.

DATA AVAILABILITY STATEMENT

Research data are not publicly available. But it is possible to share data with editors and reviewers.

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KEYWORDS Myocardial infarction, Infarct size, Cardioprotection, Quercetin

APPENDIX A. SUPPLEMENTARY DATA Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2023.08.004.