PharmacologyOnLine

Newsletter • 2021 • vol.3 • 157-169

Treatment-induced changes in the quality of life of patients with myocardial infarction combined with comorbid critical ischemia of lower extremities

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Abstract

Assessment of health-related quality of life (QOL) in patients with severe comorbidities is not only an important criterion to assess the patient's clinical status but also a factor to determine treatment approaches. This category includes patients with acute coronary syndrome (ACS) combined with critical ischemia of lower extremities (CILE). The aim of the study is to assess time-dependent changes of quality of life parameters in patients with MI combined with obliterating atherosclerosis of major vessels at the stage of critical ischemia of lower extremities and at high risk for cardiac complications at the inpatient stage of treatment. The authors have assessed 35 patients (the main group) with ACS (MI) combined with critical ischemia of lower extremities (CILE) due to atherosclerotic stenosis in the arteries of the iliac-femoral segment who received additional treatment with an L-arginine/L-carnitine combination in a setting of stenting of infarction-dependent coronary artery. The patients in the reference group (32 patients) received only standard per-protocol treatment. Apart from general clinical assessments and laboratory and instrumental tests, the patients had ultrasonography of aorto-iliac and femoral arterial segments and quality of life assessments using the EQ-5D-5L questionnaire. The results of the study: At baseline, there were no significant differences in the severity of clinical status in patients of both groups. Their clinical status was caused by typical manifestations of ACS and CILE; the patients assessed their quality of life with relatively low scores (26.14±10.13 and 25.68±10.15 conditional units [CU], respectively). The use of a course of intravenous infusions of arginine-carnitine mixture against the background of per-protocol treatment schedule in patients of the main group has led to a 100% elimination of the angina syndrome and a reduction in acute heart failure (AHF) functional class to Class I-II. The patients of the reference group receiving standard of care treatment still had chest discomfort in 5 days (53.1% of the patients) and AHF Class Killip II-III (50.0% of the patients). Time-dependent changes of troponin and creatine phosphokinase levels in patients of both groups suggested cessation of cardiomyocyte necrosis already in the first days of treatment. However, when arginine-carnitine mixture was used, the levels of necrotic biomarkers have reached reference values already on Day 5, while in the patients of the reference group the levels of these biomarkers have significantly decreased but have not reached normal. The investigational multi-modality treatment was also found to be significantly clinically superior in terms of reperfusion arrhythmias and signs of acute

heart failure, which were documented in 14.3% vs 31.6% patients in the main group and in the reference group, respectively; ventricular tachycardia and ventricular fibrillation were 3 times less frequent in patients of the main group. The suggested treatment schedule was documented to have no any adverse influence on the course of comorbidities and CILE.

The time-dependent changes in clinical status and the parameters of laboratory and instrumental tests have been positive, which was supported by the patients' assessments of their quality of life. Thus the patients with ACS combined with CILE who received standard of care treatment reported that their well-being and quality of life index improved by 40.2%. At the same time, after a course of investigational multi-modality treatment, the respective patients had significantly better improvements in quality of life assessments. Their quality of life index improved by an average of 160.9% and reached 86.5±8.3 CU. Analysis of individual QOL domains in patients with ACS and CILE in the main group has shown the best results in terms of patient-reported retrosternal pain/discomfort and anxiety/depression as well as significantly lower motor activity, which can be attributed to per-protocol limitations of physical rehabilitation program in these patients at this in-patient stage. At the same time, the use of standard of care treatment was accompanied by a significant regression in pain and some improvement in motor activity. However, the severe general clinical status of patients in this group was contributing to increasing signs of anxiety and depressive behaviors.

Key words: acute coronary syndrome; critical ischemia of lower extremities; diagnosis; treatment; quality of life.

Introduction

According to official statistics, the incidence of coronary heart disease (CHD) in Ukraine is 34.9% and the main cause of CHD-associated death and disability is MI, of which more than 50 thousand cases are registered every year [1, 2]. That being said, in spite of certain diagnostic advances and implementation of modern treatment schedules for patients with MI, the mortality rate in Ukraine remains at 10.4–17.0% [3-5], which is much higher compared to Europe and the United States and suggests insufficient consideration of all the possible links in the pathogenesis of MI, especially when MI is combined with other medical conditions or with multifocal atherosclerosis (MFA). Consequently, the available treatment programs do not accommodate potential reasonable areas of therapeutic effect.

The incidence of MFA detection varies from 18% to 54%, reaching 90% in patients with CHD [6-7]. More than 50% of such patients are admitted to the hospital with involvement not only of the coronary vessels, but usually also with obliterating atherosclerotic involvement of arteries in other territories, including those in the lower extremities [8]. Thus, according to European registries, obliterating atherosclerosis of major and peripheral blood vessels is diagnosed in more than 3% of the entire population [9-10]. The number of cases of critical ischemia of the extremities is 50-100 persons per 100 thousand population, and 5-year survival in patients with MFA does not exceed 50%, while in coronary atherosclerosis this parameter is 80-85% [9, 11]. This fact is attributed to a more severe and complicated course of comorbid disease, limitations of invasive coronary procedures and contraindications to active cardiac interventions [12-15].

It is the restricted possibilities of using highly effective early invasive coronary interventions in patients with acute coronary syndrome (ACS) combined with MFA that determine the approaches to pharmacological support in preparation for surgical interventions and prevention of complications in the perioperative and postoperative periods. One of the promising strategies for prevention of reperfusion-related complications in such patients is correction of energy metabolism disorders and ischemic damage in both cardiomyocytes and the tissues of lower extremities by using metabolic and cytoprotective therapy.

Also note that the severity of clinical manifestations of MI combined with CILE, which are associated with ischemic cardiac pain and lower extremity pain, a sharp decline in exercise tolerance, pronounced self-care deficits, psycho-emotional deterioration, as well as the adverse effects of prolonged exposure to various pharmacologicals in such patients substantiate the importance and expediency of assessing the integrated quality of life parameter as a criterion for efficiency and expediency of the therapeutic measures. The main QOL assessment instrument includes standardized questionnaires, which have been developed using psychometric methods and are specific to a particular disease [16-17]. Such specific QOL questionnaires for patients with cardiovascular disease (including MI survivors) include the EQ-5D-5L questionnaire proposed by an international interdisciplinary research task force, the EuroQol Group (1990) [18].

The aim of the study

To assess time-dependent changes of quality of life parameters induced by metabolic therapy using the EQ-5D-5L questionnaire in patients with MI combined with obliterating atherosclerosis of major vessels at the stage of critical ischemia of lower extremities and at high risk for cardiac complications at the inpatient stage of treatment.

Methods

The study was conducted as an open, controlled, comparative, parallel group study, which was based on an assessment of 67 patients with ACS (MI) combined with critical ischemia of lower extremities (CILE) due to stenotic atherosclerosis of the iliac-femoral arterial segment (chronic arterial ischemia of the III-IV degree according to the classification by B.V. Pokrovskyi and R. Fontaine [19]). The patients were distributed into two groups depending on the treatment program used. The main study group enrolled 35 patients where ACS (MI) has developed against the backdrop of critical ischemia of lower extremities. These patients had emergency balloon angioplasty and stenting of infarction-dependent coronary artery. In addition to standard drug therapy, the patients received L-arginine/L-carnitine

combination, i.e. Tivor-L by Yuria-Pharm LLC; marketing authorization No. UA/15067/01/01). The drug product was used as intravenous infusions at 100 ml once a day for 7 days. The reference group enrolled 32 patients with ACS combined with CILE who also had urgent balloon angioplasty and stenting of infarction-dependent coronary artery; these patients received standard of care per-protocol treatment according to the Unified Clinical Protocol and Adapted Clinical Guideline [20, 21]. Most of study subjects were males (87.5%) of productive age (57.54±8.02 years of age on average).

The diagnosis of acute coronary syndrome was verified according to the guidelines in the Unified Protocol of the MoH of Ukraine and ESC (2017) [20, 21]. The criteria included the presence of a typical anginal attack, respective EKG/Echo-KG changes and the signs of necrosis-resorption syndrome, and were confirmed by the findings of emergency coronary angiography. The diagnosis of obliterating atherosclerosis of major vessels of lower extremities was confirmed using clinical and laboratory assessments (pain intensity, weak or absence of pulse in lower extremity arteries; shin and thigh muscle hypotrophy; the presence of trophic changes in the area of toes and feet, etc.) and imaging studies (ultrasonography and CT angiography of major vessels).

In addition to general clinical assessments, laboratory tests and instrumental assessments (hematology and serum biochemistry, lipid panel, coagulogram, MB fraction of creatine phosphokinase (CPK-MB), troponin T, oxygen saturation of arterial blood (SpO_2), EKG in 12 standard leads with monitoring of rhythm and conductivity disorders) and assessment of intracardiac hemodynamics with transthoracic Echo-KG (Canon Aplio 400 with a sector scanner) in M-mode, B-mode and Doppler mode, the authors have surveyed all patients using the EQ-5D-5L questionnaire proposed by an international interdisciplinary research task force, the EuroQol Group [18]. This questionnaire is based on assessment of five critical quality of life domains: mobility, self-care, usual activities (activities of daily living), pain/discomfort and anxiety/depression. Each domain is divided into 5 levels depending on the subjective severity of a sign. Using an analogue scale of 0 to 100 points, the patient provides a subjective score of their health status within the range, where 0 is the lowest possible level, and 100 is the highest possible level.

Selective polypositional coronary angiography (CAG) was performed using the technique by M. Judkins (equipment: SIEMENS Axiom Artis, Germany) to assess the degree of narrowing of the lumen of infarction-dependent coronary artery, the site of stenosis and the number of affected blood vessels using the SS I and SS II scales. The severity of anatomical involvement of the coronary artery was determined using the SYNTAX scale: the score of ≤ 22 points corresponded to mild anatomical lesions, 23–32 points corresponded to moderate anatomical lesions and the score of ≥ 33 points corresponded to severe anatomical lesions.

The morpho-functional status of aorto-iliac and femoral arterial segments was assessed by ultrasonography using a linear probe (at 5 to 15 MHz). The authors assessed the patency of the artery, the diameter and the state of its lumen/walls, as well as systolic and diastolic blood flow velocity, peripheral resistance index, pulsatility index and systolic to diastolic ratio (S/D), which characterizes the status (elasticity) of the arterial wall.

In addition, all patients were assessed for the risk of in-patient mortality and 6-month mortality on the GRACE scale [22]. The risk was considered very high in presence of refractory angina, Killip Class III-IV AHF, life-threatening ventricular arrhythmias or unstable hemodynamics at the time of hospital admission (in presence of the these signs, the patients require an emergency invasive treatment within the first 2 hours post-admission); high risk was defined as > 140 points on the GRACE scale (early invasive treatment within 24 hours is indicated); moderate risk was defined as 140-109 points (late or delayed invasive treatment within 72 hours is recommended) and low risk was defined as < 109 points (invasive treatment is not indicated).

The previously mentioned examinations were performed when the patient was admitted for treatment, and again on Day 10 directly after the endovascular intervention.

Statistical processing of findings was performed using the methods of variation statistics. The samples were checked for normal distribution of data using the

Shapiro-Wilk test; both parametric (Student's t-test) and nonparametric (Mann-Whitney u-test) methods were used. In order to assess the correlation between the signs, the correlation coefficient (r) and its significance criterion using Pearson's method were determined.

Results

At baseline (when admitted for treatment), a typical algesic course of ACS was found in 85.7% and 84.4% of patients in the main study group and in the reference group, respectively; in the rest of the patients, the course was atypical (p>0.05). Pronounced general weakness was reported by 65.7% and 62.5% of study subjects, respectively; approximately 35% of patients in both groups reported chest discomfort and dyspnea/shortness of breath. Nausea, vomiting and dizziness was reported by 11.4% and 6.3% of patients in respective groups. We will also note that 100% elimination of angina syndrome was attained in course of either investigational multi-modality treatment or standard of care treatment in patients of both groups already during the first day of treatment. However, the residual symptoms of general weakness, chest discomfort, etc. were observed in 37.1% of patients in the main group and in 53.1% of patients in the reference group.

Apart from the angina syndrome, the patients in both groups were diagnosed with AHF of different severity classes (according to T. Killip, J. Kimball). Clinical manifestations of heart failure included complaints of dyspnea at rest or with insignificant physical activity (i.e. moving in the bed, self-care) in 33 (94.3%) patients in the main group and in 32 (100%) patients in the reference group, respectively (p>0.05). Palpitations were reported by 29 (82.8%) patients in the main group and by 26 (81.3%) patients in the reference group (p>0.05). The combined treatment with inclusion of a course of intravenous infusions of arginine-carnitine mixture had a substantial positive effect on clinical manifestations of acute heart failure in these patients; there also was a substantial reduction in the incidence and the severity of AHF symptoms and most patients with Killip Class III and Class II improved to Killip Class I. In the meantime, in the majority of patients in the reference group on standard of care treatment, and in 5 days of observation, 37.5% of the patients were diagnosed with Killip Class II AHF, 12.5% of the patients were diagnosed with Killip Class III AHF and 6.3% were diagnosed with Killip Class IV AHF, which suggested an insufficient therapeutic effect of standard of care treatment in comorbid patients.

In analysis of the incidence of comorbid conditions and comorbidities, which could have a substantial effect on the course of underlying disease, it was found that the most frequent conditions in patients of both study groups were hypertension (in 85.7% and 84.4% of the patients, respectively) and type 2 diabetes mellitus (in 34.3% and 34.4% of the patients, respectively). ACS was frequently developing against the backdrop of excessive body weight or obesity, which were diagnosed in 15 (42.8%) patients in the main group and in 10 (31.3%) patients in the reference group. Less frequent comorbidities included chronic obstructive pulmonary disease (COPD) (17.1% and 15.6%, respectively), chronic kidney disease (20.0% and 18.8%, respectively) and thyroid dysfunction (in 11.4% and 12.5%, respectively).

The combined treatment with inclusion of arginine-carnitine combination had a substantial effect on the severity of individual risk factors of CHD. Thus, in course of the first to the fifth day of treatment in patients with ACS combined with CILE of the main group, failure to reach normotension was reported in 25.7% of cases vs. 37.5% of cases in the reference group and failure to reach euglycemia was reported in 11.4% and 15.6% of the patients, respectively.

The time-dependent progress of left ventricular remodeling and myocardial contractility were assessed with calculation methods using Echo-KG source data obtained before and after the use of respective treatment schedules. In the meantime, it has been established (see Table 1) that patients of the main group had positive changes in LVMM and LVMMI parameters and a simultaneous significant reduction of LV wall thickness (p<0.05) in the process of treatment, which was accompanied by a substantial increase in myocardial reserve index in patients in the main group (by 13.5% vs. by 5.9% in the reference group). However, the aforementioned parameters have not reached normal values, exceeding normal 1.35-fold, while abnormal eccentric LV remodeling has increased in 68.6% of the patients.

The special characteristics of cardiac remodeling found during the study may explain a significant increase in the volumes of cardiac chambers and a pronounced reduction of both systolic and diastolic function at baseline (according to the relaxation type). During the investigational multi-modality treatment in patients with ACS combined with CILE, there was a significant reduction in LVESV, LVEDV and LAA, which led to gradual increases in EF (by 8.7%) and stroke volume (by 18.3%), as well as in cardiac contractility index (by 13.1%) ($p<0.05$) and a simultaneous substantial improvement in the parameters of LV diastolic function, namely: IVRT accelerated by 15.6% ($p < 0.05$), the E/A ratio decreased by 29.8% and early left ventricular filling delay time (DT) increased by 11.7% ($p<0.05$), which suggested the development of Type I diastolic dysfunction in patients of this group, i.e. abnormal myocardial relaxation (relaxation disorders).

We will also note that under the influence of standard of care treatment, comorbid patients only had a trend towards reduction in the size of the left ventricle and the left atrium ($p>0.05$), which was not accompanied by significant improvements in cardiac contractility (the contractility index increased by only 5.2%, and EF had a downward trend); also, escalating signs of diastolic dysfunction were present. There were increases in IVRT (by 8.5%) and DT (by 9.3%) and the respective decreases in E (by 30.4%) and E/A (by 29.1%), ($p < 0.05$). In other words, throughout the use of standard of care treatment in patients with ACS combined with CILE there had been cardiac remodeling with increasing rigidity of LV myocardium and the development of pseudo normal type of diastolic dysfunction.

The positive results of time-dependent changes in echocardiographic parameters (which have been obtained with the use of the investigational multi-modality treatment schedule using the arginine-carnitine combination) have been attained specifically due to the cardiometabolic effect of L-carnitine on inotropic heart function and the effect of L-arginine on endothelial function of blood vessels.

At baseline, disorders of cardiac rhythm and conductivity were diagnosed based on the results of EKG monitoring in 33 (94.3%) patients of the main group and in 30 (93.8%) patients of the reference group. The most frequently documented abnormalities included ventricular or supraventricular premature ventricular contractions (in, respectively, 29 (82.8%) patients of Group I and in 27 (84.4%) patients of Group II; paroxysms of atrial fibrillation (in, respectively, 13 (37.1%) and 11 (34.4 % and 5 (13.2%)); ventricular tachycardia (in 4 (11.4%) and 3 (9.4%, blocks of various degree and localization (in 14 (40.0%) and 12 (37.5%)), ($p>0.05$).

With the use of either standard of care or investigational multi-modality treatment, positive time-dependent changes in terms of the incidence of disorders of rhythm and conductivity have been documented in patients of both groups. However, a significantly higher number of arrhythmias was still observed on Day 1–Day 5 of treatment in the group of patients on standard of care treatment. Thus, in the group of patients receiving standard of care treatment, long/short QT syndrome was diagnosed almost 3 times more often (in 25.0% of cases vs. 8.6% in the group of investigational multi-modality treatment). Of note, the majority of researchers associate these syndromes with a higher risk of life-threatening ventricular arrhythmias. In a setting of standard of care treatment, ventricular tachycardia was 3 times more frequent, and ventricular fibrillation/atrioventricular block was 2.5 times more frequent compared to patients receiving arginine-carnitine mixture. In addition, the patients in this group were at significantly higher risk of developing reperfusion syndrome seen as various arrhythmias and acute heart failure (in 31.6% of patients vs. 14.3% of patients in the main group, $p<0.05$). Among patients of the main group, there were no cases of alveolar pulmonary edema, acute stent thrombosis or dissection of the intima of a coronary artery. In general, the number of complications in the early reperfusion period was 2.9 times lower in patients of the main group than in the group of patients receiving standard of care treatment.

According to EKG and Echo-KG data, the most frequently diagnosed findings in patients of both groups included injuries in the posterior phrenic cardiac compartments (42.9% and 40.6%, respectively); somewhat less frequent injuries were documented in the septoapical segment (40.0% and 34.4%, respectively) and in the lateral (basal) segment (17.1% and 25.0%, respectively). Combined or multivascular injuries were noted in 57.1% and

53.1% patients of respective study groups. That being said, hemodynamically significant stenotic lesions of the coronary artery (i.e. stenosis more than 50% of the blood vessel's diameter) were found in 97.1% of patients in the main group and in 96.9% of patients in the reference group.

It is known that manifestations of necrosis-resorption syndrome and their severity are not only important diagnostic criteria of myocardial damage, but also the early prognostic signs of potential complications and the severity of MI course. This is why these signs often inform the programs of treatment and cardiac rehabilitation in patients with ACS (MI). We monitored the progress of the necrosis-resorption process by the changes in the levels of cardiac specific enzymes (troponin T and MB fraction of creatine phosphokinase); the process of necrosis zone's replacement with fibrous tissue (fibrosis of the postinfarction scar) was monitored by the changes in fibronectin levels.

In the meantime, it has been established that time-dependent changes in troponin T and CPK-MB in patients of both study groups suggested cessation of necrosis formation in cardiomyocytes already in the first days of either standard treatment (percutaneous coronary intervention with angioplasty of infarction-dependent coronary artery and its stenting) or combined ACS treatment with additional use of arginine-carnitine mixture. Already on day five of combined treatment, the levels of troponin T and CPK-MB in most patients with ACS combined with CILE have decreased and reached reference values. At the same time, the patients in the reference group (on standard of care treatment) had significant reductions in the levels of the aforementioned parameters. However, these parameters have not returned to normal in these patients. In both study groups of patients with ACS combined with CILE, increased serum levels of fibronectin were associated with intensified myocardial fibrosis formation, as suggested by a significant fibronectin increase, i.e. by 19.0% ($p<0.05$). After investigational multi-modality treatment, fibronectin levels in patients of the main group have substantially decreased ($p<0.05$), while in the reference group fibronectin levels had an upward trend, which suggested enhanced fibrosis formation in the myocardium.

Therefore, assessment of time-dependent changes in the clinical course of this comorbidity, as well as the positive changes in the biomarkers of cardiac necrosis and fibrosis formation under the influence of investigational multi-modality treatment with inclusion of a course of intravenous infusions of arginine-carnitine mixture suggest sufficient efficacy of this treatment for ACS (STEMI). Moreover, in no case did we document any adverse influence of the suggested treatment schedule on the course of comorbidities and CILE.

In order to perform an objective efficacy assessment of the proposed combined treatment and its patient-reported perceptions, we have assessed time-dependent changes in quality of life using a standardized EQ-5D-5L questionnaire. At baseline (when admitted for treatment), the patients in both study groups gave their quality of life a relatively low score, 26.14±10.15 CU and 25.68 CU on average (Table 2). Therefore, the results provided inform a conclusion about the relatively identical low self-reported quality of life in patients of both groups, which suggests a clinical homogeneity of study groups.

During assessment of time-dependent quality of life changes during standard of care treatment in patients with ACS combined with CILE, a substantial improvement of well-being has been observed; an overall improvement in quality of life index was 40.2%. At the same time, please note significantly higher quality of life scores in patients after a course of investigational multi-modality treatment (i.e. with an additional course of intravenous infusions of the arginine-carnitine mixture); in these patients, the quality of life index improved by an average of 160.9% and became significantly higher compared with the group of comorbid patients (i.e. ACS combined with CILE) who received conventional standard of care treatment ($p<0.05$).

During analysis of survey results in terms of individual quality of life domains of the EQ 5D-5L questionnaire, special attention was focused on assessment of motor activity, pain/discomfort and anxiety/depression. The "I have no problems" response was reported for the above three QOL criteria only in patients with ACS and CILE who additionally received a course of intravenous infusions of arginine-carnitine mixture. The best results were obtained in terms of patient-reported

assessment of retrosternal pain/discomfort (HR = 0.42 [95% CI 0.24-0.75; p<0.05]) and anxiety/depression (HR = 0.52 [95% CI 0.28-0.92; p<0.05]). The significantly lower indices of motor activity in patients of that group (HR = 0.74 [95% CI 0.62-1.07; p<0.05]) can be attributed to per-protocol limitations of their physical rehabilitation at the hospital stage.

At the same time, the use of standard of care treatment in comorbid patients with ACS combined with CILE was accompanied by a significant regression in pain intensity (HR = 0.64 [95% CI 0.46-0.87; p<0.05]) and by some improvement in motor activity (HR = 0.76 [95% CI 0.54-0.98; p<0.05]). However, the severe general clinical status of patients in this group led to enhanced signs of anxiety and depressive behaviors at the end of their in-patient treatment (HR = 0.87 [95% CI 0.66-1.19; p<0.05]).

Therefore, the analysis of time-dependent changes of quality of life under the influence of investigational multi-modality treatment and standard of care treatment supports their efficacy in both study groups; also, assessment of time-dependent changes of patient-reported subjective quality of life using a standardized EQ-5D-5L questionnaire is a sufficiently valid and highly sensitive criterion to evaluate the efficacy of treatment schedules [23]. However, the conventional treatment schedule appeared insufficiently effective in comorbid patients with ACS combined with CILE; only additional use of intravenous infusions of arginine-carnitine mixture was able to produce a significant (3.4-fold) improvement of quality of life in patients of the main study group.

The results obtained in a comprehensive assessment of clinical and functional status in patients with ACS combined with obliterating atherosclerosis of lower extremities and critical ischemia allow us concluding that emergency endovascular intervention (i.e. coronary artery angioplasty and stenting of infarction-dependent coronary artery) is the treatment of choice in these comorbid patients. However, the severe baseline clinical status and its further deterioration in peri- and postoperative period after percutaneous coronary intervention is often accompanied by the development of reperfusion syndrome with various duration and severity of left ventricular failure and disorders of rhythm and conductivity, which provided the rationale for additional treatment with inclusion of L-arginine and L-carnitine. Under the influence of such treatment, a substantial reduction in the incidence of disorders of rhythm and conductivity was noted already on the second day of observation. Also, after the end of the course of treatment in patients of this group, the incidence of arrhythmias decreased by 53.1%, and the manifestations of acute heart failure reduced by 44.2%.

The positive result of treatment with arginine-carnitine combination was achieved specifically due to the effect of L-carnitine on the inotropic heart function. L-carnitine is playing an important role in energy metabolism in the myocardium due to transfer of free fatty acids from the cytosol inside the mitochondria and thereby ensuring the bioavailability of a high-energy substrate for oxidative metabolism in cardiomyocytes [24, 25]. In addition to that, by facilitating oxidation of long-chain fatty acids and by modulating the CoA/CoA-SH ratio, this compound is taking part in binding of acyl residues in peroxisomes and mitochondria and has a positive influence on amino acid metabolism by assimilating the pool of free radical compounds. This ensures stabilization of organelles and cellular membranes and prevents accumulation of fatty acid esters in the cytoplasm of cardiomyocytes, which may lead to fatal ventricular arrhythmias [26-28].

The use of L-arginine (which is acting as an active regulator of intermediate metabolism and energy supply processes and is the main substrate for nitric oxide synthesis) has contributed to restoration of functional status of vascular endothelium, which ensured adequate levels of microcirculation in organs and tissues of the body [24, 29]. Moreover, many studies have demonstrated that the post-stenting use of L-arginine reduced the number of restenoses due to its antihypoxic, antioxidant and membrane-stabilizing effects [30-32].

In addition, the study findings allow us concluding that clinical manifestations, as well as health-associated physical and functional changes in the body, have a substantial effect on quality of life parameters, which are one of the most important assessment criteria for the severity of patient's condition, the need for revascularization interventions and additional drug treatment in

comorbid patients with MI combined with CILE due to atherogenic stenosis in the arteries of the iliac-femoral segment. The potential to improve QOL in such comorbid patients with clinical and laboratory/instrumental signs of treatment efficacy, in part by using revascularization interventions and drug therapy suggests the expediency of including intravenous infusions of arginine-carnitine mixture in the combination treatment schedule for patients with MI combined with CILE.

Conclusions

1. The use of a course of investigational multi-modality drug therapy with inclusion of L-arginine and L-carnitine in pre- and postoperative period in patients with ACS combined with obliterating atherosclerosis and critical ischemia of lower extremities was leading to improved clinical status and recovery of central and peripheral hemodynamics, reduced incidence of reperfusion arrhythmia (by 53.1%) and acute heart failure (by 44.2%), which was accompanied by a significant improvement in the quality of life index.

2. Patients with ACS and CILE who additionally received a course of intravenous infusions of arginine-carnitine mixture had significantly better results in terms of patient-reported assessment of relief of retrosternal pain/discomfort (HR = 0.42 [95% CI 0.24-0.75; p<0.05]), reduction in anxiety/depression (HR = 0.52 [95% CI 0.28-0.92; p<0.05]) and improvement of motor activity (HR = 0.74 [95% CI 0.62-1.07; p<0.05]).

Acknowledgments The authors declare that there are no conflicts of interest.

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Table 1. Treatment-induced time-dependent changes of cardiac remodeling and central hemodynamics in patients with ACS/MI and CILE with investigational multi-modality treatment (M ± m)

Parameter		Day 1	Day 5	Day 10	p^1	p^2	p^3
1		2	3	4	5	6	7
LVMM, g	1	283.8±8.2	254.2±9.2	248.6±10.2	<0.05	>0.05	<0.05
	2	278.9±9.6	237.6±9.4	235.3±10.1	<0.05	>0.05	<0.05
LVMMI, g/m²	1	182.6±5.42	158.1±5.12	156.8±5.15	<0.05	>0.05	<0.05
	2	182.1±4.84	142.2±5.21	134.6±5.35	<0.05	>0.05	<0.05
LVRWT	1	0.41±0.02	0.41±0.02	0.39±0.01	>0.05	>0.05	>0.05
	2	0.43±0.02	0.39±0.02	0.37±0.01	>0.05	>0.05	<0.05
RMRI	1	0.51±0.01	0.49±0.01	0.48±0.02	>0.05	>0.05	>0.05
	2	0.52±0.01	0.48±0.01	0.45±0.01	<0.05	>0.05	<0.05
LVEDV, ml	1	156.7 ± 1.2	155.6 ± 1.4	154.4 ± 1.4	>0.05	>0.05	>0.05
	2	154.9 ± 1.3	133.8 ± 1.5	134.2 ± 1.4	<0.05	>0.05	<0.05
LVESV, ml	1	89.2 ± 2.6	86.5 ± 2.8	86.8 ± 3.1	>0.05	>0.05	>0.05
	2	89.3 ± 2.3	82.1 ± 2.4	81.9 ± 2.3	<0.05	>0.05	<0.05
LAA, cm²	1	39.8 ± 1.3	35.7 ± 1.4	36.9 ± 1.3	>0.05	>0.05	>0.05
	2	39.7 ± 1.2	34.3 ± 1.3	32.4 ± 1.2	<0.05	>0.05	<0.05
CI	1	0.92±0.02	0.96±0.03	0.97±0.03	>0.05	>0.05	>0.05
	2	0.93±0.02	1.03±0.02	1.07±0.02	<0.05	>0.05	<0.05
EF, %	1	46.9 ± 0.4	43.2 ± 0.4	43.8 ± 0.5	<0.05	>0.05	>0.05
	2	46.3 ± 0.4	51.5 ± 0.3	53.5 ± 0.6	<0.05	<0.05	<0.05
IVRT, ms	1	80.6 ± 1.3	86.3 ± 1.3	88.1 ± 2.1	<0.05	>0.05	<0.05
	2	80.7 ± 1.1	93.1 ± 1.4	95.6 ± 2.1	<0.05	>0.05	<0.05
DT, ms	1	239.8 ± 5.1	255.4 ± 5.2	264.4 ± 4.8	>0.05	>0.05	<0.05
	2	239.7 ± 4.2	271.6 ± 4, 7	284.7 ± 4.6	<0.05	>0.05	<0.05
E, cm/s	1	65.5 ± 1.8	53.2 ± 1.7	45.6 ± 1.6	<0.05	<0.05	<0.05
	2	65.4 ± 1.3	51.6 ± 1.4	43.7 ± 1.4	<0.05	<0.05	<0.05
A, cm/s	1	43.3 ± 1.2	47.2 ± 1.2	42.8 ± 1.1	<0.05	<0.05	>0.05
	2	43.6 ± 1.1	48.6 ± 1.2	44.7 ± 1.1	<0.05	>0.05	>0.05
E/A	1	1.51 ± 0.04	1.13 ± 0.04	1.07 ± 0.04	<0.05	<0.05	<0.05
	2	1.51 ± 0.05	1.06 ± 0.06	0.98 ± 0.05	<0.05	>0.05	<0.05

Notes: 1). 1, 2 = the parameters in patients with ACS and CILE, respectively, in a setting of standard treatment (n=32) and multimodality treatment (n=35);

2). p1, p2, p3 = the respective differences in parameters between the patients on Day 1 and Day 5 of treatment, between the patients on Day 5 and Day 10 of treatment and between the patients on Day 1 and Day 10 of treatment;

3). The underlined values are significantly different from the data in the reference group (p<0.05).

Abbreviations: A = peak filling velocity with atrial systole; CI = contractility index; DT = early left ventricular filling delay time; E = peak early left ventricular filling velocity; EF = ejection fraction; IVRT = isovolumic relaxation time; LAA = left atrium area; LEDV = left ventricular end-diastolic volume; LESV = left ventricular end-systolic volume; LVMM = left ventricular myocardium mass; LVMMI = left ventricular myocardium mass index; LVRWT = left ventricular relative wall thickness; RMRI = residual myocardial reserve index;

Table 2. The influence of investigational multi-modality treatment schedule on time-dependent changes of quality of life parameters in patients with ACS combined with CILE (M ± m)

Stage of treatment	**Patients with ACS and CILE +Arginine-Carnitine**	**Patients with ACS and CILE + standard of care treatment**	**P**
On admission, CU	25.68±9.74	26.14±10.15	>0.05
Prior to discharge, CU	86.48±8.33	43.72±9.24	<0.05
The increase index during treatment, %	+160.88	+40.22	<0.05
Note: The underlined values are significantly different from the baseline data; p = the significance of the difference between the values before and after treatment.			