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ORIGINAL PAPER

PROGNOSTIC FACTORS INFLUENCING ALL-CAUSE MORTALITY AND HOSPITALIZATIONS AFTER INPATIENT CARDIAC REHABILITATION FOR ACUTE CORONARY EVENTS

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Abstract

Introduction. The comprehensive cardiac rehabilitation (CR) program is essential to improve outcomes.
The objective of the study was to identify the prognostic factors for all-cause mortality and hospitalizations during 12 months after inpatient CR for an acute cardiac event and to investigate the impact of a supervised home-based CR program on these outcomes.
Material and methods. The study included 449 patients with coronary artery disease who completed the institutional CR program and were divided into 2 groups after discharge: CR(+) group – supervised home-based CR program (186 patients) and CR(-) group – 263 patients who were not supervised. The follow up period was 12 months.
Results. The all-cause mortality rate one year after inpatient CR was 5.7%. Prognostic factors for mortality were age, heart failure (HF) NYHA III, HF with reduced ejection fraction (HFrEF), pulmonary congestion at discharge, length of stay in the intensive care unit and CR department. The hospitalization rate was 40.3%. The prognostic factors for hospitalizations

Résumé

Facteurs pronostiques pour la mortalité et les hospitalisations après réhabilitation cardiaque pour événements coronariens aigus

Introduction. Un programme durable de réabilitation cardiaque (RC) est essentiel pour améliorer le pronostic.
L'objectif de l'étude a été d'identifier les facteurs pronostiques de la mortalité et des hospitalisations pendant 12 mois après la RC institutionnel pour un événement cardiaque aigu et étudier l'impact d'un programme de RC supervisé à domicile.
Matériel et méthodes. L'étude a inclus 449 patients avec insuffisance cardiaque (IC) ischémique qui ont accompli le programme de RC institutionnel et ont été divisés en 2 groupes: RC(+) – RC supervisé à domicile pendant 12 mois (186 patients) et RC(-) – 263 patients qui n'étaient pas surveillés.
Résultats. Le taux de mortalité un an après la RC institutionnel était de 5,7%. Les facteurs pronostiques de mortalité étaient l'âge, IC NYHA III, IC avec fraction d'éjection réduite (ICFEr), la congestion pulmonaire

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were HF NYHA III, HFrEF, N-terminal pro-B-type natriuretic peptide (NT-proBNP), left ventricular ejection fraction, pulmonary congestion at discharge, Charlson comorbidity index and duration of hospitalization in the CR department. In the CR(+) group the mortality (3.22% vs 7.6%, p<0.05) and hospitalization rate (34% vs 48.3%, p<0.01) were lower than in the CR(-) group.
Conclusions. In our study, age, HF features, pulmonary congestion at discharge, length of stay in intensive care unit and CR departments were identified as main prognostic factors for all-cause mortality and hospitalizations during one year after institutional CR. The all-cause mortality and hospitalization rate were lower in patients who completed the supervised home-based CR program.

Keywords: all-cause mortality, hospitalizations, myocardial revascularization, cardiac rehabilitation.

List of abbreviations

AIDS – acquired immunodeficiency syndrome
AMI – acute myocardial infarction
CAD – coronary artery disease
CABG – coronary artery bypass grafting surgery
CCI – Charlson comorbidity index
CKD – chronic kidney disease
CKD-EPI- Chronic Kidney Disease Epidemiology Collaboration
CPET – cardiopulmonary exercise test
CR – cardiac rehabilitation
ESC – European Society of Cardiology
eGFR – estimated glomerular filtration rate
ICU – intensive care unit
HF – heart failure
HFpEF – heart failure with preserved ejection fraction
HFmrEF – heart failure with mildly reduced ejection fraction
HFrEF – heart failure with reduced ejection fraction
LV – left ventricle
LVEF – left ventricular ejection fraction
MI – myocardial infarction
NT-proBNP – N-terminal pro-B-type natriuretic peptide
NYHA – New York Heart Association
PTCA – percutaneous transluminal coronary angioplasty
VAS – Visual Analog Scale
VO_2 – oxygen uptake
6MWT – 6 minutes walking test

à la sortie, la durée du séjour en unité de soins intensifs et de RC. Le taux d'hospitalisation était de 40,3%. Les facteurs pronostiques des hospitalisations étaient IC NYHA III, ICFEr, le fragment N-terminal du peptide natriurétique cérébral (NT-proBNP), la fraction d'éjection, la congestion pulmonaire à la sortie, l'indice de comorbidité Charlson et la durée d'hospitalisation pour RC. Dans le groupe RC(+), la mortalité (3,22% vs 7,6%, p<0,05) et les hospitalisation (34% vs 48,3%, p<0,01) étaient inférieurs à ceux du groupe RC(-).
Conclusions. L'âge, les caractéristiques de IC, la congestion pulmonaire à la sortie, la durée d'hospitalisation dans l'unité de soins intensifs et RC ont été identifiés comme facteurs pronostiques pour mortalité et hospitalisations pendant un an après la RC institutionnel. Le taux de mortalité et d'hospitalisation étaient inférieurs aux patients qui ont accompli la RC supervisé à domicile.

Mots-clés: mortalité toute cause, hospitalisations, revascularisation myocardique, réabilitation cardiaque.

Introduction

Cardiovascular diseases cause approximately one-third of deaths worldwide. Among cardiovascular illnesses, coronary artery disease (CAD) ranks as the most prevalent[1-3]. An increasing number of individuals with non-fatal CAD live with chronic disabilities and impaired quality of life[1,4].

Cardiac rehabilitation (CR) is a multidisciplinary intervention, whose core components include patient assessment, management and control of cardiovascular risk factors, physical activity counselling, prescription of exercise training, dietary advice, psychosocial management and vocational support[5]. Evolving over time, it is currently a comprehensive patient-tailored program that aims to improve the patient's physical, psychological, social and work condition, after an acute cardiac event or in the context of chronic cardiovascular disease with risk factors or incomplete revascularization[6]. CR has received the highest class of recommendation and level of evidence in chronic heart failure (HF) therapy[7], after acute coronary syndrome[8] and after myocardial revascularization[9].

The efficacy of CR to reduce mortality, hospitalization rate, myocardial infarction (MI) prevalence was demonstrated in multiple studies and meta-analyses[10-13]. Also, a survival benefit for patients receiving CR after an acute coronary syndrome was found (26% reduction of cardiac mortality, 18% reduction of recurrent hospitalization) with a proven cost-effectiveness[11-13]. CR participation is associated with about 40% reduced mortality after coronary artery bypass grafting surgery (CABG)[11]. CR improves exercise capacity and health-related quality of life through direct physiological effects of exercise training, risk factor control, lifestyle behaviour and improving adherence to a medical treatment regimen[10,11].

CR is a multicomponent evidence-based complex intervention that provides important benefits to the patients with HF and is Class I/level A evidence[7], thus it should be the fifth pillar in HF management alongside drug and device therapy[14]. The European Society of Cardiology (ESC) Heart Failure III Registry highlights exercise CR program as one of numerous interventions that are effective in HF sub-populations, but are complex, expensive, scarce and/or otherwise difficult to implement[15]. There are over 1500 CR programs across Europe, existing in 90% of countries. However, there is only one spot for every seven patients in need. Program delivery is highly consistent with European CR guidelines, although there is significant regional variation in relation to funding sources, costs to patients, the nature of providers on CR teams, dose and alternative model delivery[16].

Referring to the phase II of CR, the impact of centre-based CR is substantially limited by significant underuse among eligible patients[17]. Thus, in United States between 2007 and 2011 only 10.3-16.3% of eligible patients participated in CR after hospitalization for MI, percutaneous transluminal coronary angioplasty (PTCA) or CABG[18]. New CR delivery strategies are needed for the >80% of eligible patients and one potential approach is alternative site- or home-based CR. In concept, home-based CR could help overcome some of the access-related barriers that centre-based CR programs face[16].

The European Society of Cardiology (ESC) Atlas of Cardiology emphasizes that between 1990 and 2019 the median age-standardized prevalence estimates for cardiovascular disease per 100,000 inhabitants recorded a modest increase in 15 middle-income countries, inclusive Republic of Moldova, where 593.8 primary PTCA and 101.6 CABG per million people are registered[19].

The objective of the study was to identify the prognostic factors that influence all-cause mortality and hospitalization rate during 12 months after completing the institutional CR program for CABG or an acute myocardial infarction (AMI) with/without PTCA, and also to highlight the impact of a supervised home-based CR program on mortality, hospitalizations, HF evolution and quality of life.

Materials and methods

The features of the cardiac rehabilitation program

Based on the National Clinical Protocol on Cardiovascular Rehabilitation[20], all patients with AMI or cardiac surgery are eligible to complete phase I of CR in the hospital, this service being covered by the National Medical Insurance Company. The CR program consisted of 1) daily physical training prescribed by a cardiologist and a physiotherapist according to the patient risk group; 2) patient education, which consists in informing the patient about the disease, the cardiovascular risk factors and their self-care principles, 3) psycho-emotional assistance, 4) nutritional counselling, 5) optimal pharmacological optimal treatment and 6) cardiovascular risk factors correction. At discharge, they receive a patient guide with recommendations on continuing the CR program at home. Under the conditions of the current public health system from our country in the first 12 months after the acute cardiac event, all patients perform CR at home, having a monthly visit to the family doctor, and, if necessary, they are visited at home by the nurse. Patients who present complications or deterioration

of their health condition usually are referred to the territorial district medical institution for ambulatory cardiology consultation or for hospitalization.

Study design and participants

The research is a prospective analytical study, carried out in a national tertiary level centre. Initially, 1315 patients who completed the institutional CR program in our hospital during 2020-2022 were selected. Further, 579 subjects without CAD were excluded. From the 736 patients with CAD, 290 were excluded due to the lack of data about their condition at the end of the study. Finally, 449 patients with CAD who completed the institutional CR program and who gave their consent to participate in the research were selected (Figure 1). Thus, the inclusion criteria for our study were age >18 years, diagnosis of CAD, completion of the institutional CR program after an acute cardiac event. The exclusion criteria are the following: refusal to participate in the study, lack of information about the patient's condition after 12 months from discharge.

Written informed consent was obtained from all the subjects involved in the study. The study was conducted in accordance with the Declaration of Helsinki of 1975 as revised in 2000 (5) and was approved by the Ethics Committee of the Institute of Cardiology, Chisinau, Republic of Moldova, protocol No. 3 from 04/03/2020.

The cohort of patients was divided into 2 groups: CR(+) group (186 patients) and CR(-) group (263 patients) (depending on the ability to travel to the CR centre, the availability to receive phone calls, the patient's preference). CR(+) group performed partially supervised CR at home during a 12 months follow up period, applying the method of structured telephonic support for remote supervision by the study group cardiologist. Thus, CR(+) patients were

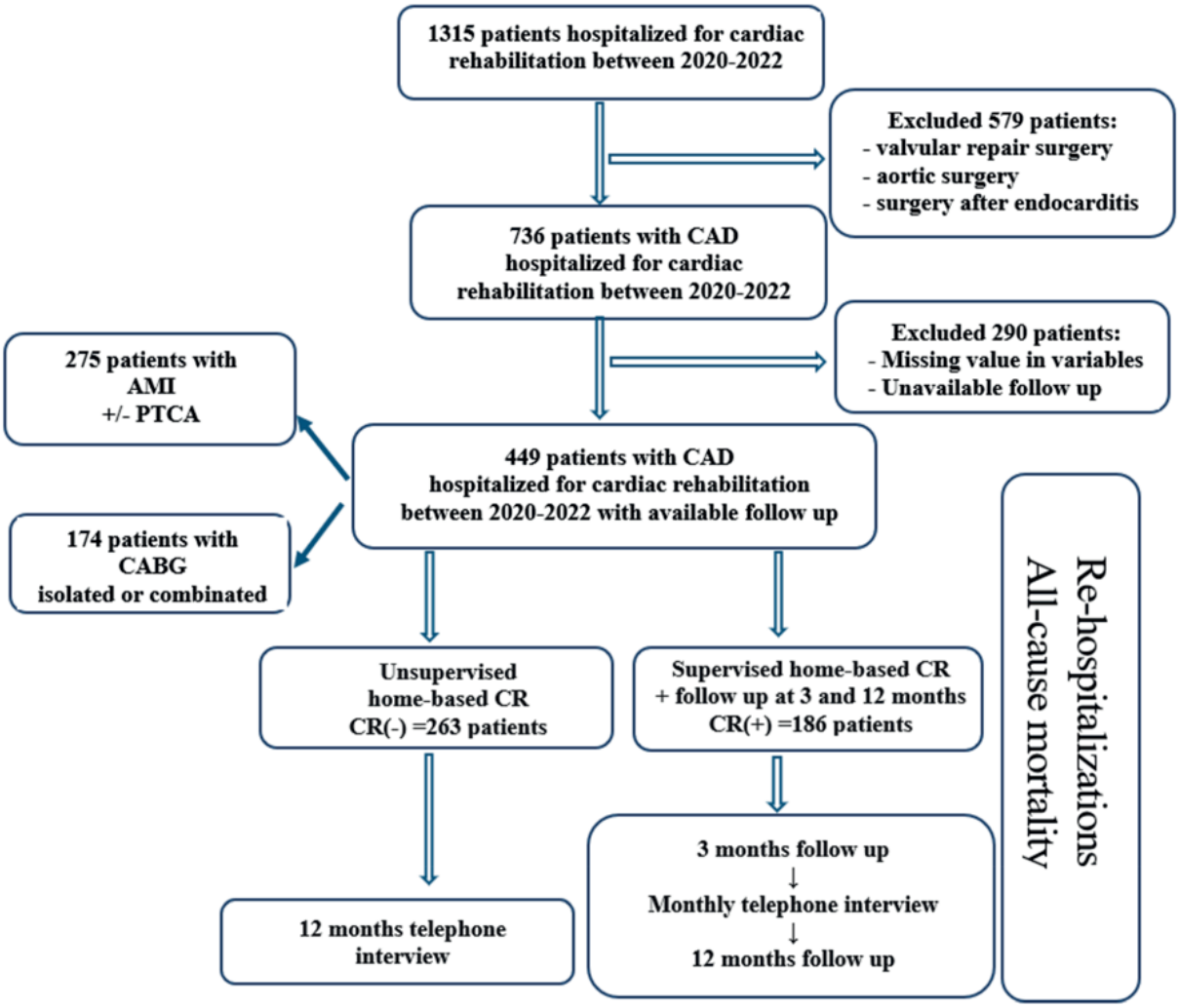


Figure 1. Flow chart of the study.
Note: AMI – acute myocardial infarction, CABG – coronary artery by-pass grafting, CAD – coronary artery disease, CR – cardiac rehabilitation, PTCA – percutaneous transluminal coronary angioplasty.

contacted monthly by phone to be questioned about their health condition, adherence to drug treatment and physical training, side effects, complications.

During the follow-up period, each patient from the CR(+) group was evaluated by a cardiologist specialized in CR at 3 and 12 months after finishing the inpatient CR program. The clinical examination, electrocardiographic and echocardiographic evaluation, laboratory analysis (including the evaluation of N-terminal pro-B-type natriuretic peptide – NT-proBNP), evaluation of exercise capacity through the 6 minutes walking test (6MWT) and the cardiopulmonary exercise test (CPET), assessment of quality of life through Euro-QoL 5D-5L (Euro-Quality of Life 5 dimensions- 5 levels) questionnaire were performed during the 3 and 12 months follow up visits. As a result of the listed investigations, the patient's general condition was assessed, cardiovascular risk factors were evaluated and recommendations were issued about the adjustment of the optimal pharmacological treatment, long-term physical training program at home, the nutrition regimen and risk factors control.

Patients in the CR(-) group followed the usual care protocol for patients after an acute cardiac event (described above), performing unsupervised CR at home, and 12 months after they were contacted for long-term follow-up based on patient-centred outcome obtained by telephone interview.

Patient assessment methods

Transthoracic echocardiography was performed on a Mindray echocardiography machine and was based on a well-established protocol aimed at evaluating the morphological and functional cardiac characteristics, with an emphasis on the assessment of left ventricular (LV) systolic function and its remodelling parameters. Among the laboratory analyses, the following were evaluated: blood count, lipidogram, NT-proBNP, kidney function and estimated glomerular filtration rate (eGFR) according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. CPET was a symptom-limited test performed on an electronic cycle ergometer (Cosmed Quark CPET) according to an incremental protocol with a workload of 20 W/min by patients who had no contraindications. The 6MWT was performed by measuring the distance achieved by the patient in 6 minutes walking on a flat ground with the determination of heart rate, blood pressure and oxygen saturation before and after the test. The Charlson comorbidity index (CCI) was used to quantify the patients' comorbidities, according to the 17 items: age, myocardial infarction, congestive HF, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease (CKD), solid tumor, leukemia, lymphoma, AIDS. Also, CCI allowed us to assess the estimated probability of the patient's survival related to the present comorbidities. The EuroQoL 5D-5L questionnaire was used to assess the quality of life which includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and 5 levels of appreciation for each dimension. The EuroQoL 5D-5L questionnaire also includes a Visual Analog Scale (VAS), by which respondents can report their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status).

Statistical analysis

The statistical analysis was obtained using IBM SPSS v22 software (IBM Corp, Amonk, NY). Quantitative variables were expressed as mean and standard error, and qualitative variables were presented as percentages. The student T-test was used to compare the quantitative variables and the chi-squared test was used to evaluate the differences between the qualitative variables between the groups of deceased/surviving and hospitalized/non-hospitalized patients. The assessment of the prognostic factors was carried out by determining the odds ratio and the confidence interval. Discriminant analysis was used to assess the prognosis. Statistical significance was considered at p-value <0.05.

Results

General characteristics of the patient cohort

The study included 449 patients with CAD who completed the institutional CR program after an acute cardiac event. Among them, 275 subjects (61.2%) suffered AMI (with/without PTCA) and 174 patients (38.7%) underwent isolated or combined CABG surgery in the context of chronic coronary disease. All patients with AMI were investigated by coronary angiography, in 87.4% of subjects the culprit lesion of the coronary artery was addressed by PTCA. In 12.5% of patients, it was not possible to perform PTCA for various reasons (the need for surgical revascularization or late referral to the doctor). The average age within the cohort was 63.6±0.4 years, the majority being men (76.9%).

All-cause mortality

The all cause-mortality rate within 1 year after inpatient CR for an acute cardiac event was 5.7% (26 patients). Among deceased patients, 47.6% died suddenly, in 19% the cause of death was HF and in 4.8% stroke. Non-cardiovascular diseases were the cause of death in 19% of patients (Figure 2).

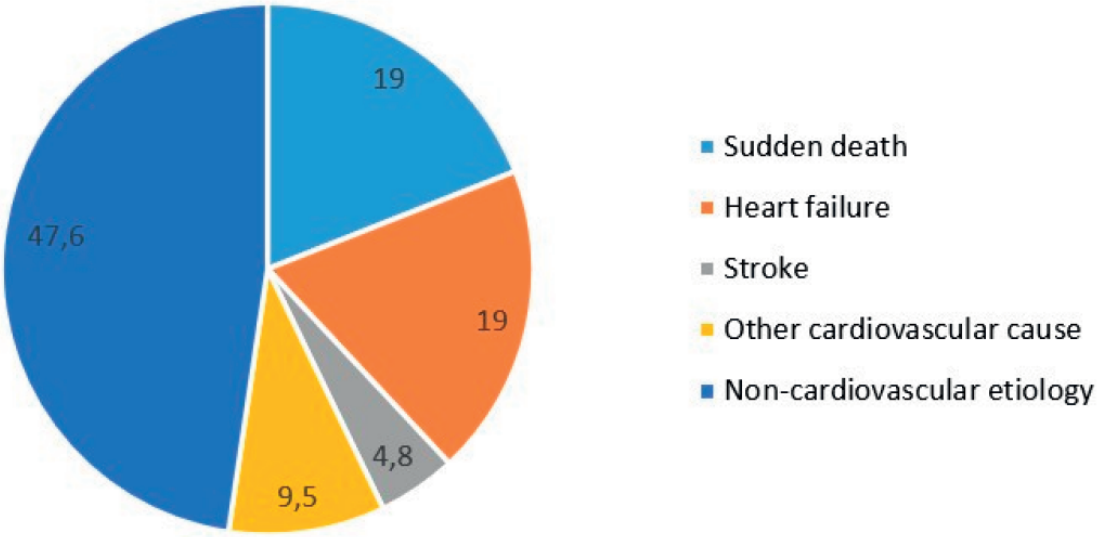


Figure 2. The structure of all-cause mortality in the cohort of patients with CAD within 1 year after institutional cardiac rehabilitation.

Table 1 shows the general characteristics of the group of patients who died compared to those who survived during 12 months after completing the inpatient CR program. The mean age of the deceased patients was 69.12±2.39 years, of which 69.2% were men. Thus, deceased subjects were older ($p<0.05$) and more overweight ($p<0.05$). Among those with myocardial revascularization by CABG, deceased patients frequently underwent complex combined surgery ($p<0.001$). Acute HF with a more advanced Killip class in the early period after the cardiac event ($p<0.01$) or NYHA (New York Heart Association) III functional class (FC) ($p=0.001$) and signs of congestive HF at discharge were determined more often in this group. The rate of patients with HF with reduced ejection fraction (HFrEF) was higher ($p<0.05$). The left ventricular ejection fraction (LVEF) average value was 37.7±1.9% compared to surviving subjects, 43.9±0.5% ($p<0.01$). The mean value of NT-proBNP recorded in the group of deceased patients was significantly higher, 4512.4±1627.5 pg/mL ($p<0.05$).

Table 2 reflects the in-hospital management of deceased patients and highlights a significantly longer length of stay in the intensive care unit (ICU) ($p<0.05$), while the duration of the overall hospitalization was similar. The duration and specifics of the CR program did not differ from the surviving patients, although the exercise capacity expressed by peak oxygen uptake (VO_2peak) determined during CPET was reduced in the deceased patients ($p<0.05$).

Among comorbidities, the rate of CKD was statistically significantly higher in deceased patients ($p<0.01$), next to superior CCI in these subjects ($p<0.01$) (Table 2).

After a thorough analysis of all clinical and paraclinical factors, 4 more relevant parameters were identified: the patients' age, previous myocardial infarction, duration of hospitalization in the ICU and length of stay in the CR department (Tables 1 and 2). The discriminant analysis, using these 4 variables, allows the correct prediction of death during 12 months after the acute cardiac event (AMI with/without PTCA or CABG) in 69.2% of cases.

The prognostic factors that influence mortality in patients with CAD during a 12-months follow-up period after the inpatient CR program for an acute cardiac event were HF NYHA III (OR=4.0, 95% CI 1.77-6.23), HFrEF phenotype (OR=1.988, 95% CI 1.145-3.451), persistence of pulmonary congestion at discharge (OR=3.558, CI 95% 1.168-5.948), longer duration of hospitalization in the CR department (OR=1.198, CI 95% 1.049-1.368) and in the ICU (OR=1.287, CI 95% 1.052-1.575), age (OR=1.082, 95% CI 1.03-1.135) (Figure 3).

Hospitalizations during 1 year after inpatient CR for an acute cardiac event

The rate of patients hospitalized for any cause in the first year after the acute cardiac event was 40.3%. The average number of cardiovascular hospitalizations was 1.73±0.1 per patient, with a mean duration of 11.2±1.0 days. The average number of hospitalizations for non-cardiovascular causes in the same period was 1.18±0.07, with a duration of 11.6±1.3 days.

The patients hospitalized during the first year after an acute cardiac event had a similar age and gender distribution to those not hospitalized. The type of myocardial revascularization also did not

Table 1. General characteristic of patient groups divided according to mortality and hospitalizations during one year after the acute cardiac event.

	Mortality			*Hospitalizations*		
Parameter	*Survivors*	*Deceased*	*p*	*Non-hospitalized*	*Hospitalized*	*p*
Men, %	79.8%	69.2%	0.149	81.0%	77.9%	0.254
Age, years	63.0±0.4	69.1±2.3	<0.05	62.7±0.56	63.4±0.6	0.401
Age group, %						
25-44 years, %	2.4	0		2.1	3.3	
45-59 years, %	38.7	46.2	<0.001	32.1	49.2	<0.001
60-74 years, %	53.6	26.9		61.2	41.4	
75-90 years, %	5.3	26.9		4.6	6.1	
Body weight, kg	86.1±1.0	106.3±7.0	<0.05	87.7±4.7	87.3±4.8	0.954
BMI, kg/m^2	29.6±0.3	34.2±2.2	0.096	29.9±0.9	31.9±1.6	0.303
Abdominal circumference, cm	108.2±0.8	117.5±3.3	<0.05	99.8±4.7	101.3±6.5	0.856
Smoking status, %						
non-smoker	38.9	53.3	0.209	38.7	39.5	0.927
former smoker	45.2	46.7		44.5	45.7	
smoker	15.9	0		16.8	14.8	
Type of coronary atherosclerotic lesion, %						
monovascular	11.6	4.0	0.735	11.7	9.7	0.664
bivascular	17.9	12.0		20.0	15.3	
trivascular	65.8	76.0		62.6	69.3	
multivascular	4.7	8.0		4.8	4.5	
Type of MRev, %						
surgical	44.2	30.8	0.087	41.1	47.2	0.130
percutaneous	55.8	69.2		58.9	52.8	
Type of heart surgery, %						
Isolated CABG	34.5	0	<0,001	38.1	31.3	0.345
CABG + aortic valve replacement	14.4	12.5		16.3	11.3	
CABG + mitral valve prosthesis/plasty	21.9	37.5		22.8	20.0	
CABG + aneurysmectomy	1.7	12.5		2.2	1.3	
CABG + aneurysmectomy + valve repair	27.0	37.5		20.7	36.3	
AMI with MRev, %	86.3	88.5	0.161	87.0	71.4	<0.05
AP after MRev, %	24.5	34.6	<0.01	23.7	24.5	0.744
Acute HF, %						
Killip I	57.6	21.1	<0,01	58.0	53.1	0.327
Killip II	35.5	68.4		34.5	37.8	
Killip III	5.7	5.3		4.2	8.2	
Killip IV	1.1	5.3		2.4	0	
NYHA FC of HF at discharge, %						
NYHA II	74.8	42.3	0.001	81.4	66.1	<0.01
NYHA III	25.3	57.7		18.9	33.9	

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	Mortality			Hospitalizations		
Parameter	*Survivors*	*Deceased*	*p*	*Non-hospitalized*	*Hospitalized*	*p*
HF phenotype, %						
HFpEF	36.0	12.5	<0,05	39.0	31.7	<0.01
HFmrEF	31.2	33.3		34.4	24.8	
HFrEF	32.8	54.2		26.6	41.5	
LV EF, %	43.9±0.5	37.7±1.9	<0.01	46.3±1.3	38.3±1.3	<0.01
Previous myocardial infarction, %	30.7	37.1	<0.05	33.1	42.5	<0.05
Previous coronary angioplasty, %	18.8	3.8	<0.05	16.5	22.7	0.281
LV aneurysm, %	15.2	18.2	0.447	12.6	18.4	0.101
Atrial fibrillation/flutter, %	23.0	26.9	0.675	23.0	23.9	0.884
PVC, %	3.1	7.7	<0.01	3.6	4.4	0.817
VT, %	2.4	15.4	<0.01	2.5	3.9	0.406
Pericardial effusion, %	16.9	26.7	<0.001	14.8	20.0	<0.05
Rx pulmonary venous congestion at discharge, %	17.3	42.9	<0.05	12.0	24.5	<0.05
NT-proBNP, pg/ml	2864.9±278.7	4512.4±1627.5	<0.05	2080.5±691.4	5091.0±1126.8	<0.05
Hemoglobin, g/L	139.1±0.7	127.1±4.2	<0.01	137.9±1.7	136.3±1.5	0.074
eGFR, mL/min/1.73m^2	79.8±1.3	62.8±7.1	<0.05	83.0±2.1	76.7±3.4	0.735
Total cholesterol, mmol/l	5.1±0.07	4.9±0.2	0.389	5.5±0.1	5.2±0.1	0.635
LDL-cholesterol, mmol/l	3.1±0.06	2.9±0.1	0.355	3.2±0.1	3.2±0.1	0.143

AMI – acute myocardial infarction, AP – angina pectoris, BMI – body mass index, CABG – coronary artery by-pass grafting, eGFR – estimated glomerular filtration, FC- functional class, HF – heart failure, HFpEF – heart failure with preserved ejection fraction, HFmrEF – heart failure with mildly reduced ejection fraction, HFrEF – heart failure with reduced ejection fraction, LDL-cholesterol – low density lipoprotein cholesterol, LV – left ventricle, LV EF – left ventricular ejection fraction, MRev – myocardial revascularization, NT-proBNP – N-terminal pro b-type natriuretic peptide, NYHA – New York Heart Association, PVC – premature ventricular contractions, Rx – radiography, VT – ventricular tachycardia

Table 2. In-hospital management and comorbidities of patient groups stratified by mortality and hospitalizations during one year after the acute cardiac event.

	Mortality			Hospitalizations		
Parameter	*Survivors*	*Deceased*	*p*	*Non-hospitalized*	*Hospitalized*	*p*
Length of stay in the ICU, days	2.2±0.06	3.5±0.5	<0.05	2.2±0.08	2.4±0.1	0.196
Length of stay in the specialized ward (after surgery or AMI), days	8.1±0.1	8.1±0.7	0.963	7.7±0.2	8.6±0.2	<0.05
Duration of hospitalization for the acute cardiac event, days	10.2±0.2	11.2±0.8	0.295	9.8±0.2	10.9±0.3	<0.01
Length of stay in the CR department, days	7.1±0.1	8.7±0.6	0.077	7.2±0.1	7.7±0.1	<0.01
Cardiac rehabilitation program:						
Risk stratification before the CR program			0.063			<0.01
Moderate risk	65.5	48.0		72.1	55.5	
High risk	34.5	52.0		27.9	44.5	
Continuous walking the day before discharge, m	519±11.6	476.0±46.3	0.369	541.0±15.6	487.7±16.9	<0.05
Kinetotherapy sessions performed	5.48±0.07	5.35±0.2	0.628	5.4±0.09	5.5±0.1	0.235
The distance performed at 6MWT, m	305.4±6.0	308.0±36.3	0.947	321.4±8.6	289.2±8.0	<0.01
VO_2 peak, ml/min	1501.7±80.0	1171±29.6	<0.05	1249.1±42.2	1083.5±38.1	<0.05

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	Mortality			Hospitalizations		
Parameter	*Survivors*	*Deceased*	*p*	*Non-hospitalized*	*Hospitalized*	*p*
Comorbidities:						
Arterial hypertension, %	85.7	88.5	0.909	85.1	86.7	0.609
Stroke, %	6.9	3.8	0.935	7.2	6.6	0.303
Diabetes mellitus, %	36.9	38.5	0.689	36.4	37.0	<0.05
COPD, %	7.0	15.4	0.261	5.5	8.9	0.216
Pleural effusion, %	2.8	12.0	<0.001	1.7	4.0	0.306
Hypostatic pneumonia, %	2.8	20.0	<0.01	2.3	4.0	0.287
CKD (st III-V K-DOQI), %	50.4	56.5	<0.01	13.2	15.6	0.115
CCI, %						<0.05
without comorbidities	2.6	0		3.0	1.9	
1 comorbidity	34.9	33.3	0.861	36.7	32.1	
≥2 comorbidities	55.4	53.3		56.8	51.9	
≥5 comorbidities	7.8	13.3		3.5	14.1	
CCI cardiovascular, %						<0.01
without cardiovascular comorbidities	4.9	0		5.1	4.8	
1 cardiovascular comorbidity	61	53.3	0.466	66.7	49.5	
≥2 cardiovascular comorbidities	34.1	46.7		28.3	45.7	
CCI, score	3.67±0.09	4.67±0.3	<0.01	3.64±0.1	3.7±0.1	0.732
CCI – 10 years estimated survival, %	57.21±1.63	32.27±7.7	<0.01	59.5±1.9	53.4±2.8	0.087

AMI – acute myocardial infarction, CCI – Charlson comorbidity index, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease, CR – cardiac rehabilitation, ICU – intensive care unit, K-DOQI – Kidney Disease Outcomes Quality Initiative, 6MWT – the 6-minute walking test, VO_2 peak- peak oxygen uptake

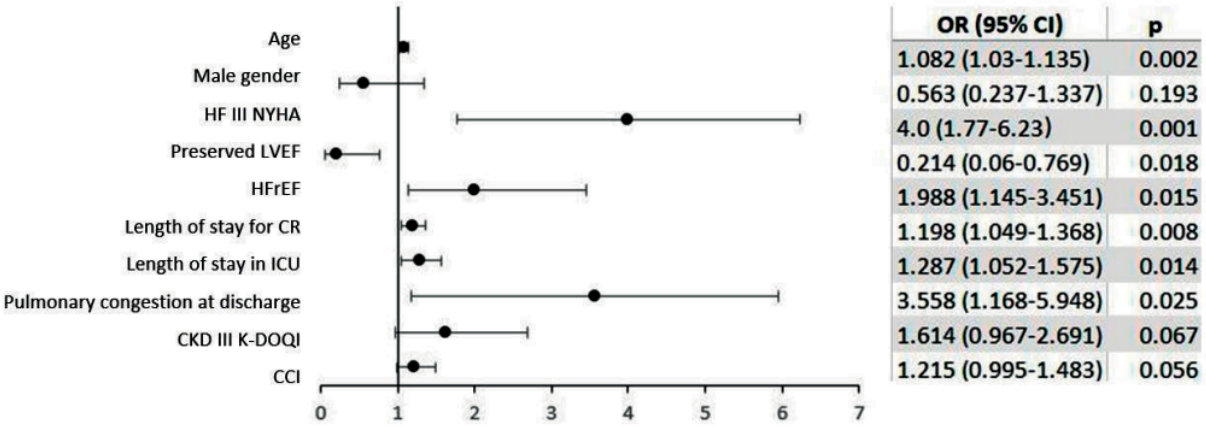
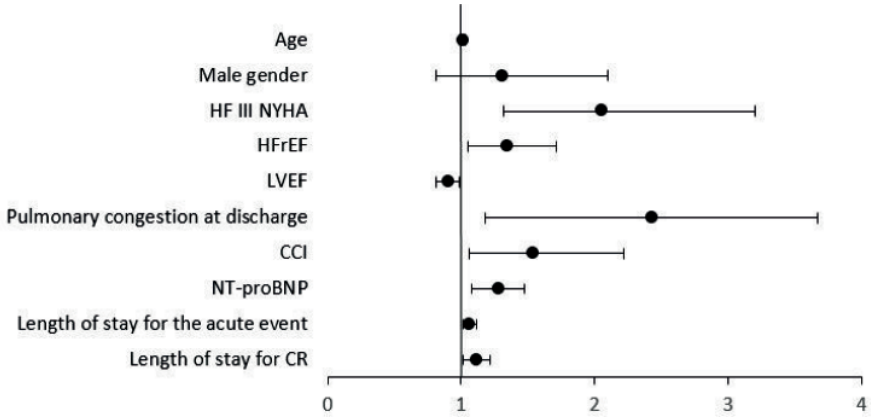


Figure 3. Prognostic factors for mortality in patients with CAD during the 12 months follow-up period after inpatient CR program for an acute cardiac event.
Note: CCI- Charlson Comorbidity Index, CKD- chronic kidney disease, CR- cardiac rehabilitation, HF- heart failure, HFrEF- heart failure with reduced ejection fraction, ICU- intensive care unit, LVEF- left ventricular ejection fraction, NYHA- New York Heart Association.

differ between the two groups. In contrast, hospitalized patients had more advanced chronic HF (NYHA III 33.9% vs 18.9%, p<0.01; HFrEF 41.5% vs 26.6%, p<0.05; NT-proBNP 5091.0±1126.8 pg/mL vs 2080.5±691.4 pg/mL, p<0.05) (Table 1).

The patients hospitalized during the 12 months after completing the inpatient CR program also had a longer length of stay both in the specialized department (p<0.05) and in the CR department (p<0.01). The exercise capacity, expressed by VO_2peak at CPET



	OR (95% CI)	p
Age	1.012 (0.989-1.035)	0.305
Male gender	1.310 (0.817-2.103)	0.262
HF III NYHA	2.054 (1.317-3.205)	0.002
HFrEF	1.342 (1.051-1.712)	0.018
LVEF	0.904 (0.813-0.989)	0.014
Pulmonary congestion at discharge	2.427 (1.184-3.670)	0.015
CCI	1.535 (1.065-2.214)	0.022
NT-proBNP	1.278 (1.083-1.476)	0.04
Length of stay for the acute event	1.064 (1.014-1.117)	0.011
Length of stay for CR	1.114 (1.017-1.221)	0.02

Figure 4. Prognostic factors for hospitalizations during the 12 months follow-up period after inpatient CR program for an acute cardiac event in patients with CAD.
Note: CCI- Charlson Comorbidity Index, CR- cardiac rehabilitation, HF- heart failure, HFrEF- heart failure with reduced ejection fraction, LVEF- left ventricular ejection fraction, NYHA- New York Heart Association, NT-proBNP- N-terminal pro-B type natriuretic peptide

and by the distance performed during the 6MWT, was reduced in the group of hospitalized patients. The CCI highlights an increased prevalence of patients with a greater number of comorbidities, including two or more cardiovascular comorbidities, in this group, p<0.05. Among the comorbidities taken separately, the rate of patients with diabetes mellitus was higher in the hospitalized group (p<0.05) (Table 2).

The following prognostic factors for hospitalizations during the 12 months follow-up period in patients with CAD after inpatient CR program for an acute cardiac event were identified: HF NYHA III (OR=2.054, 95%CI 1.317-3.205), HFrEF phenotype (OR=1.342, 95%CI 1.051-1.712), higher level of NT-proBNP (OR=1.278, 95%CI 1.083-1.476), persistence of pulmonary congestion at discharge (OR=2.427, 95%CI 1.184-3.670), LVEF (OR=0.904, 95%CI 0.813-0.989), higher CCI value (OR=1.535, 95%CI 1.065-2.214), longer hospitalization for CR (OR=1.114, 95%CI 1.017-1.221) (Figure 4).

The impact of supervised home-based CR on the main outcomes: mortality, hospitalizations, HF evolution and quality of life

Table 3 highlights the particularities of the groups of patients depending on the attendance of the supervised home-based CR program during 12 months after discharge.

The all cause-mortality rate within 12 months after the acute cardiac event was lower in the CR(+) group, 3.22%, vs CR(-) group, 7.6% (p<0.05). The hospitalization rate was 34% in the group of patients who were supervised during 12 months, being lower compared to the CR(-) group (48.3%), p<0.01. The average number of hospitalizations due to cardiovascular causes was lower in the CR(+) group (1.48±0.1 vs 1.99±0.1, p<0.05), the duration of hospitalization was also reduced (9.5±0.9 vs 12.9±1.1, p<0.05). Although the number of hospitalizations for non-cardiovascular causes was similar regardless of participation in the supervised home-based CR program, their length of stay was also shorter in CR(+) patients (9.31 vs 14.01, p<0.05).

A positive evolution of the HF features in the CR(+) group during 12 months follow up was observed, the rate of patients with NYHA II and preserved LVEF being higher in this group (p<0.001), registering a 8.3% increase in the average LVEF.

Evaluating the patients' quality of life 12 months after the acute cardiac event through the Euro-QoL 5D-5L questionnaire, it was observed that CR(+) patients obtained benefits by improving the dimensions "Self-care" and "Pain/discomfort". The self-assessment of the perceived health status using the Visual Analog Scale revealed a significantly higher value in the CR(+) group.

Discussion

According to our research results, the supervised home-based CR program was beneficial in terms of hospitalization rate, HF evolution and some aspects of the quality of life.

In our study, the rate of women included in the research was 23.1%, without a significant difference in mortality or hospitalizations rate during the first year after the acute event. Other researchers have also noted that the participation rate of women in the CR program, especially outpatient CR, is much lower, often less than 15%[11,17,21]. Eijsvogels et al.

Table 3. Patient endpoints according to participation in the supervised home-based CR program for 12 months after the acute cardiac event.

Parameter	*CR(–)*	*CR(+)*	*p*
Age, years	63.0±0.6	64.1±0.5	0.087
Male gender, %	81.2	76.4	0.094
Type of MRev, %			<0.001
CABG	36.8	56.1	
PTCA	63.2	43.9	
HF at discharge:			
NYHA FC, %			0.05
NYHA II	54.6	39.7	
NYHA III	45.4	59.8	
LV EF,%	44.4±1.2	43.1±0,6	0.124
HF phenotype, %			0.359
HFpEF	39.1	30.5	
HFmrEF	29.3	31.1	
HFrEF	31.6	36.4	
HF at 12 months follow up:			
NYHA FC, %			<0.001
NYHA II	68.2	82.8	
NYHA III	31.7	17.2	
LV EF,%	43.1±11.0	51.4±9.6	<0.001
HF phenotype, %			<0.001
HFpEF	33.8	70.2	
HFmrEF	19.2	11.6	
HFrEF	47.0	18.2	
Outcomes:			
Mortality rate, %	7.6	3.22	<0.05
Hospitalization rate, %	48.3	34.0	<0.01
Cardiovascular hospitalizations	1.99±0.1	1.48±0.1	<0.05
Days of hospitalization due to a cardiovascular cause, days	12.90±1.1	9.51±0.9	<0.05
Non-cardiovascular hospitalizations	1.25±0.08	1.10±0.06	0.136
Days of hospitalization due to a non-cardiovascular cause, days	14.01±1.9	9.31±0.7	<0.05
Quality of life – Euro-QoL 5D-5L			
Mobility	1.6±0.7	2.21±1.0	<0.001
Self-care	1.46±0.6	1.17±0.4	<0.001
Usual activities	2.03±0.8	2.1±0.9	0.170
Pain/discomfort	1.64±0.7	1.55±0.7	0.201
Anxiety/depression	1.79±0.8	2.6±0.8	<0.001
EQ VAS	76.4±15.1	83.0±12.3	<0.001

CABG – coronary artery by-pass grafting, CR(-) – non participants in the outpatient cardiac rehabilitation program, CR(+) – participants in the outpatient cardiac rehabilitation program, Euro-QoL 5D-5L – the 5-Level 5-Dimension EQ, HF – heart failure, HFpEF – heart failure with preserved ejection fraction, HFmrEF – heart failure with mildly reduced ejection fraction, HFrEF – heart failure with reduced ejection fraction, LV EF – left ventricle ejection fraction, MRev – myocardial revascularization, NYHA – New York Heart Association, PTCA – percutaneous transluminal coronary angioplasty, VAS – Visual Analog Scale.

demonstrated that the mortality risk reduction with CR participation in men (32.1%) and women (31.3%) is similar, suggesting that both sexes benefit equally from CR[22]. However, Kanaoka et al. showed that female sex is more frequently associated with lower mortality in the CR (+) group than male sex[21].

Older patients are often underrepresented in CR programs[21,22]. In our research, we confirmed the fact reported by other studies that the mortality rate and hospitalizations are higher among patients over 75 years old, as well as the prevalence of comorbidities. Moreover, Eijsvogels et al. demonstrated that

CR was associated with large reductions in all-cause mortality in patients aged 75 to 84 years (27.8%) and 85 years or older (32.0%). These findings suggest that CR improves survival even in older age groups, which have mortality rates of up to 63.9%[22].

In our study, the prognostic factors for mortality within 1 year after the acute cardiac event were age, HF NYHA III, HFrEF phenotype, persistence of pulmonary congestion at discharge, length of stay in the ICU and CR department. Other studies have highlighted the following parameters that significantly predict mortality: age, diabetes mellitus, low exercise capacity (<4 metabolic equivalents), 3-vessel disease, lack of complete myocardial revascularization and a low LVEF[23].

We identified several prognostic factors for hospitalizations during the 12 months follow up period after inpatient CR: HF NYHA III, HFrEF phenotype, NT-proBNP level, LVEF, persistence of pulmonary congestion at discharge, Charlson comorbidity index value and length of hospital stay in the CR department. Other studies reported low exercise capacity and the presence of diabetes mellitus as factors that independently predicted re-hospitalization[23]. A systematic review investigated the predictors of unplanned 30-day readmissions after CABG and identified the following: older adults, female, weight loss, high serum creatinine, anticoagulant use, dialysis, comorbidities, postoperative complications, prolonged length of hospital stay and mechanical ventilation[24].

Investigating the association between CR and mortality in cardiovascular diseases, it was identified that CR participation was associated with a 32-42% lower risk of all-cause mortality[10,22], 26% lower odds of hospitalization[10], 32% lower probability of developing AMI[25] and a 37% lower odds of stroke[10] compared with nonparticipation. On the other hand, a systematic review including 63 trials and 14,846 participants concluded that exercise-based CR reduces the risk of cardiovascular mortality, but not total mortality, also reduces the risk of hospitalization, but not the risk of MI or revascularization, and improves health-related quality of life[11]. A meta-analysis (85 trials, 23,430 subjects) also identified that exercise-based CR was associated with significant risk reductions in cardiovascular mortality, hospitalizations, and myocardial infarction, but did not influence the need for PTCA or CABG[26].

The prevalence of cardiovascular and non-cardiovascular comorbidities is high among patients with CAD and patients with multi-morbidity have a worse prognosis[22,27]. This fact was also found in our study, where patients who died or were hospitalized in the first year after the acute cardiac event had a higher CCI value. In this context, a study from the Netherlands demonstrated that CR participation among patients with cardiovascular disease with the highest CCI score was associated with notable risk reduction (30%)[22]. Compared to other studies, diabetes mellitus was not identified as a prognostic factor for hospitalizations and mortality in our research, but its rate was higher in the group of hospitalized (37% vs 36.4%) or deceased (38.5% vs 36.9%) patients.

We identified a significantly longer length of hospitalization in the CR department in the case of patients who required hospitalization or died in the following 12 months after an acute cardiac event. This fact is probably determined by the risk profile of these patients, considering that 52.0% of deceased patients and 44.5% of hospitalized patients were at high risk according to the risk stratification before initiation of the institutional CR program.

Our study provides additional evidence in favour of considering CR as the fifth pillar in the treatment of HF[14]. Thus, we noted a significant improvement in HF parameters during the first year after the acute cardiac event, which was more evident in patients who performed supervised home-based CR, including the improvement of NYHA FC, LVEF and HF phenotype.

A systematic review led by McDonagh et al. (24 trials, 3046 participants), who aimed to compare the effect of home-based and supervised centre-based CR on mortality and morbidity, exercise-capacity, health-related quality of life and modifiable cardiac risk factors in patients with heart disease, found no difference in total mortality, exercise capacity and health-related quality of life up to 24 months follow-up. Thus, home- and centre-based forms of CR seem to be similarly effective in improving clinical and health-related quality of life outcomes in patients after AMI, myocardial revascularization or HF[28]. Regarding morbidity data beyond 1 year, Thomas et al. found no significant between-group differences during 6 years follow up and the median time to first re-hospitalization was similar for both groups (4.49 years)[17].

According to the data of our study, the mortality rate within 1 year was lower in patients who performed remote supervised home-based CR plus intermittent follow up compared to those who were not supervised. Recent results were reported by a study including 460 participants with CAD, that evaluated the association of lower mortality and home-based CR program that was entirely remote. This research identified a 36% lower hazard of mortality among patients who participated in the home-based CR versus nonparticipants. Thus, home-based CR could be associated with a survival benefit among select patients with cardiovascular disease[29]. Also, the completion of home-based CR among referred patients was associated with

a lower risk of the combined all-cause mortality and all-cause hospitalizations up to 12 months[30].

Conclusions

According to the obtained data, the prognosis of mortality and morbidity during 12 months after completing the institutional CR program for an acute cardiac event (AMI with/without PTCA or CABG) was determined by the HF characteristics at discharge (NYHA FC, HFrEF, NT-proBNP, persistence of pulmonary congestion) in association with age, length of stay in the ICU and CR department, Charlson comorbidity index value.

The all-cause mortality rate and all-cause and cardiovascular hospitalization rate in patients who completed the supervised home-based CR program during 12 months after an acute cardiac event were significantly lower, while the evolution of chronic HF and perceived health status were more favourable.

Remote monitoring of diagnostic markers for adverse effects of physical exercises or drug treatment and intermittent follow-up, carried out under the cardiologic control, contributed to these benefits of home-based rehabilitation during the first-year program.

Author Contributions:

Conceptualization, E. V.; methodology, E. V.; software and statistical analysis, C.J.; investigation, J.C., D.L, O.P., S.D., B.D., I.G; telephonic interview, N.B., C.O., M.C.; data curation, J.C., D.L, O.P., S.D., I.G; writing–original draft preparation, J.C., D.L, O.P.; writing–review and editing, E.V., J.C.; supervision, E.V.; project administration, E.V. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law. Ethical approval was waived by the Ethics Committee of the Institute of Cardiology, Chisinau, Republic of Moldova, protocol No. 3 from 04/03/2020. Informed consent was obtained from the patients included in the study."

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