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RESEARCH LETTER
Cardiac Rehabilitation

Phase III multidisciplinary exercise-based rehabilitation is associated with fewer hospitalizations due to adverse cardiovascular events in coronary artery disease patients

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Multidisciplinary exercise-based cardiovascular rehabilitation (CR) leads to significant reductions in mortality and risk for adverse cardiovascular events in coronary artery disease (CAD) patients.[1] As a result, CR is a Class 1A intervention.[2] However, in many countries, the number of supervised CR sessions is limited due to logistic issues or reimbursement policies. The peak oxygen uptake of CAD patients, however, continues to increase when the participation in CR is prolonged,[3] and additional improvements in blood pressure, lipid profile, and glycaemic control are noticed as a result of prolonged CR.[4] We hypothesize that CAD patients may benefit from prolonged (Phase III) CR programmes, evidenced through less hospitalization and/or the prevention of premature death, which has been noticed in heart failure patients.[5] The aim of this study is, therefore, to evaluate if supervised Phase III CR in CAD patients leads to greater reductions in hospitalizations, due to adverse cardiovascular events, and mortality, when compared to a standard 3-month supervised CR programme.

In this retrospective study, files from patients who participated in a multidisciplinary exercise-based CR programme at Jessa Hospital, Hasselt, Belgium, starting from January 2013 up to January 2017, were consulted. This study was approved by the Jessa Hospital medical ethics committee. Patients with the primary diagnosis of CAD (based on angiography during an elective investigation, hospital admission because of an acute coronary syndrome, or significant ST-segment depression during exercise testing) with or without heart failure, implantable cardioverter-defibrillator and/or pacemaker, and who completed a 3-month CR programme (with the completion of at least 30 supervised exercise training sessions) within 3 months, without the re-occurrence of cardiovascular re-events within this time frame, were selected. From those patients, some continued their supervised CR, thus leading to two subgroups: a comparison group (who did not further participate in supervised CR) vs. an intervention group (who further participated in supervised CR).

At the entry of CR, age, sex, medication, cardiovascular risk factors [blood pressure, body mass index, blood lipid profile (total, high- and low-density lipoprotein cholesterol), blood glucose and glycated haemoglobin, smoking behaviour], indication for CR, peak workload capacity (W_{peak}), and peak oxygen uptake (VO_{2peak}) were recorded/assessed. The groups were case-matched at the entry of CR for body mass index, age, and sex. Hereafter, a 3-month multidisciplinary CR was started (patients were also offered consultations with a psychologist, dietician, and/or social nurse when indicated). The exercise sessions (2–3/week) consisted of 40–60 min aerobic exercises such as treadmill walking, cycling, and arm cranking.[6,7] The exercise intensity was based on the heart rate and workload, set between the first and second ventilatory threshold, and was gradually increased during the CR programme. Low-to-moderate resistance training was also implemented at an intensity and frequency tailored to each patient. After 3 months of CR, the patients from the intervention group were supported to exercise on other modalities as well (e.g. rowing, stepping) and without strict monitoring of the exercise intensity. Next, the patient records from Jessa Hospital were investigated for the re-occurrence of hospitalization due to adverse cardiovascular events [symptomatic cardiac arrhythmias (palpitations, syncope), excessive dyspnoea or orthopnoea, angina pectoris, acute myocardial infarction)] or revascularization (by percutaneous coronary intervention or bypass surgery), or death over a maximal possible follow-up duration,

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Table 1 Characteristics at the entry of cardiovascular rehabilitation and outcomes during follow-up

Variables	Comparison ($n = 87$)	Intervention ($n = 87$)	*P*-value
Age (years)	69 (2)	70 (2)	NS
Sex (*n*)	70 (♂)	70 (♂)	NS
Weight (kg)	79 (3)	80 (3)	NS
Height (cm)	172 (2)	171 (2)	NS
Cardiovascular diseases, *n* (%)			
Myocardial infarction	32 (37)	39 (45)	NS
CAD/AMI treated by			
CABG	16 (19)	22 (24)	NS
ENDO ACAB	11 (13)	6 (7)	NS
PCI	59 (68)	60 (69)	NS
Cardiovascular co-morbidities			
Heart failure	6 (7)	6 (7)	NS
Valve disease	1 (1)	7 (8)	NS
Pacemaker	4 (5)	5 (6)	NS
ICD	3 (3)	8 (9)	NS
Medication, *n* (%)			
Beta-blocker	71 (82)	65 (75)	NS
Calcium channel blocker	11 (12)	17 (19)	NS
ACE inhibitor	41 (47)	43 (49)	NS
Angiotensin II receptor antagonist	5 (6)	0 (0)	NS
Diuretic	11 (13)	29 (33)	0.044
Antithrombotic	81 (93)	84 (97)	NS
Nitrate	13 (15)	19 (22)	NS
Statin	83 (95)	75 (86)	NS
Fibrate	1 (1)	3 (3)	NS
Metformin	5 (6)	7 (8)	NS
Sulfonylurea	2 (2)	0 (0)	NS
DPP4 inhibitor	1 (1)	0 (0)	NS
Incretin	0 (0)	1 (1)	NS
Insulin	3 (3)	4 (5)	NS
Cardiovascular risk factors			
Total cholesterol (mg/dL)	170 (11)	159 (9)	NS
Triglycerides (mg/dL)	152 (22)	135 (12)	NS
LDL (mg/dL)	96 (9)	89 (8)	NS
HDL (mg/dL)	47 (3)	45 (3)	NS
Fasting blood glucose (mg/dL)	110 (4)	111 (11)	NS
HbA1c (mmol/mol)	38 (1)	39 (3)	NS
Systolic BP (mmHg)	143 (6)	144 (8)	NS
Diastolic BP (mmHg)	82 (5)	81 (3)	NS
Smoking, *n* (%)	29 (33)	22 (25)	NS
BMI (kg/m^2)	26.5 (0.9)	27.4 (0.8)	NS
Exercise capacity			
Peak workload capacity (W)	127 (10)	120 (10)	NS
Peak oxygen uptake (mL/min)	1526 (101)	1445 (100)	NS
Outcomes during follow-up			
Patients hospitalized, *n* (%)	43 (49)	30 (34)	0.046
Total hospitalization days/patient	0.91 (0.3)	0.55 (0.2)	NS
Total hospitalization days/patient/month	0.028 (0.01)	0.013 (0.005)	0.0027
Time to first hospitalization (days)	532 (156)	1038 (446)	0.0020
Days/hospitalization per patient	2.66 (1.02)	1.41 (0.56)	NS
Days/hospitalization per patient/month	0.08 (0.03)	0.03 (0.01)	0.029
Death (*n* patients)	2	6	NS

Categorical variables are expressed as proportion (%, *n*). Continuous variables are expressed as mean (SD).
ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DPP4, dipeptidyl peptidase-4; ENDO ACAB, endoscopic atraumatic coronary artery bypass; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; ICD, implantable cardioverter-defibrillator; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; SD, standard deviation.

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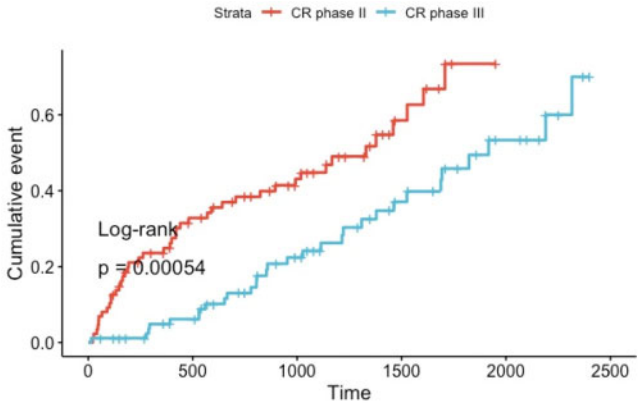

Figure 1 Kaplan–Meier curve representing time to the first hospitalization as a result of 3 months of cardiovascular rehabilitation vs. Phase III cardiovascular rehabilitation. Significantly fewer hospitalizations were noticed in coronary artery disease patients who prolonged the exercise-based cardiovascular rehabilitation beyond 3 months (blue line, intervention group) vs. coronary artery disease patients who followed a 3-month cardiovascular rehabilitation programme only [red line, comparison group, hazard ratio: 2.31 (95% confidence interval = 1.42–3.76)]. X-axis represents days of follow-up. CR, cardiovascular rehabilitation.

starting from the completion of the 3-month CR. All patients were followed by cardiologists from Jessa Hospital, so any adverse event was reported in these hospital records. In case of an adverse event with (urgent) admission to another hospital, the report of this admission was sent to and stored by, Jessa Hospital. By SAS JMP® unpaired *t*-tests were used to compare continuous variables between the groups, or χ^2 tests for nominal data, all with Bonferroni corrections for multiple comparisons (to avoid Type 1a errors). Kaplan–Meier curves were created to examine the time to the first hospitalization and a log-rank test was applied for comparison between the groups. A *P*-value <0.05 (two-tailed) was considered statistically significant.

At the entry of CR, the groups were statistically comparable (*Table 1*) on baseline variables, except for the intake of diuretics. The intake of diuretics in CAD patients is associated with an elevated mortality, and thus not in favour of the intervention group.[8] As a result of 3 months of CR, the patients experienced significant but equal increments in W_{peak} (from 127 ± 10 to 148 ± 11 W in the comparison group, from 120 ± 10 to 137 ± 11 W in the intervention group) and VO_{2peak} (from 1526 ± 101 to 1654 ± 105 mL/min in the comparison group, from 1445 ± 100 to 1654 ± 124 mL/min in the intervention group). After this phase, only the intervention group continued the multidisciplinary CR programme, in which the follow-up duration was not different between the groups (36.7 ± 3.5 vs. 42.1 ± 4.7 months in the comparison vs. intervention group) and medication prescription did not change (data not shown). In total, 42 ± 1 vs. 148 ± 31 supervised exercise training sessions were completed in the comparison vs. intervention group ($P < 0.05$). CAD patients in the intervention group had significantly fewer hospitalizations than in the comparison group [hazard ratio: 2.31 (95% confidence interval = 1.42–3.76)]. The intervention group also had shorter periods of hospitalization (by ±62%,*Table 1* and *Figure 1*). These observations align with previous studies, in which significantly greater improvements in cardiovascular risk and physical fitness were noticed as a result of prolonged CR.[3,4] Mortality was, however, not different between the groups, possibly related to the low rate of mortality generally at 4.6% in the total group (*Table 1*). The observed clinical benefits in the present study are hypothesized to be related to prolonged supervised exercise training, greater adherence to medication prescription, healthy nutrition guidelines, and better psychological coping,[9] next to the direct availability of healthcare professionals to address symptoms/questions. As a result, this study suggests that supervised multidisciplinary Phase III CR is of benefit to CAD patients. This study was limited by a small, single site, retrospective design with an inability to control for potential confounding variables. On the plus side the CAD population was strongly representative, of routine clinical practice, in terms of age and comorbidity. An explanation for the difference in diuretics intake between groups cannot be provided.

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