TITLE:

EARLY AND INTENSIVE CARDIAC REHABILITATION AFTER ACUTE MYOCARDIAL INFARCTION IN HIGH RISK PATIENTS: SAFETY, EFFICACY AND IMPACT ON PROGNOSIS.

SHORT TITLE: Russo - Cardiac rehabilitation after myocardial infarction

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ABSTRACT

Background: A large body of evidence shows that exercise-based cardiac rehabilitation (CR) after an acute myocardial infarction (MI) plays a beneficial role in modifying morbidity and mortality. Nevertheless, its use is rather scant; moreover, most of the structured exercise-based CR programmes begin relatively late after the acute event. Aim of this study was to evaluate safety, efficacy and impact of an early (within 2 weeks), in-hospital, CR after a MI on short and long term prognosis in high risk patients.

Methods: In the period 2008-2012, 376 patients (mean age 64,0±12,3 years; male 77%) were consecutively admitted to an intensive, in-hospital, CR programme, shortly after (16,4±9,9 days from event) an acute MI (ST elevation 63%). All the patients followed a structured and comprehensive rehabilitation programme, including 3 daily sessions of physical activity 6 days/week under strict physiotherapic and medical surveillance, and counselling meetings. Functional capacity was assessed by a six-minute walking test (6MWT) on admission and at discharge and by a cardiopulmonary exercise test (CPET) at the end of the CR period. To evaluate the effects of an impaired left ventricular ejection fraction (EF) on the rehabilitative process, the patients were divided into 2 groups according to an EF cut-off of 40%. A telephonic interview was assessed in order to evaluate rate of death, hospitalizations, smoke cessation, physical activity and adherence to pharmacological treatment.

Results: During the CR stay (14,5±3,1 days), no fatal events occurred and only 4 subjects (1,06%) dropped out of the programme due to non-fatal complications. At the end of the rehabilitative period all the patients showed a significant increase of physical capacity, with a gain of 70.7±55.7 m ($p<0.05$) at 6MWT, without differences between the EF groups. In the whole population cardiac mortality and all cause mortality resulted 5.0% and 8.0 % respectively at 1 year and 8.0 % and 13.0 % at 5 years. As expected, the prognosis was worse in older people and in the lower EF group. Seventy three per cent of the subjects referred to continue a regular physical activity; in the entire population an elevated therapy adherence was registered and, among addicted, 77% had definitely given up smoking.

Conclusions: An early and intensive exercise and counselling based CR, resulted to be safe and effective in high risk subjects after an acute MI. Safety was demonstrated by the lack of fatal events during Hospital stay despite the proximity to the index event, as well as by the low number of complications requiring transferral to advanced medical unit. The effectiveness was demonstrated by the significant increase in the functional capacity in the short term - independently from the residual ventricular function - and by the high adherence to the therapy and to the proposed lifestyle modifications; this may have produced a positive effect on mortality in the long term.

INTRODUCTION

Notwithstanding the favourable effects of new therapeutic approaches during the acute phase of myocardial infarction (MI) leading to very favourable short-term outcomes,[1-3] the post discharge prognosis remains still unsatisfactory:[4-6] Cardiac rehabilitation (CR) is a multidisciplinary treatment playing clearly documented beneficial effects, helpful for the vast majority of cardiac patients and universally considered an important part of secondary prevention. Although this treatment is advocated by several professional organizations and nowadays it's a class I recommendation in most guidelines,[7-10] its use remains still rather scant in Europe and in USA.[11,12]

In particular in coronary artery disease (CAD) patients, exercise-based CR has lots of valuable effects: it improves symptoms and functional capacity, reducing both morbidity and mortality.[13-15] Recently, Martin et al.[16] showed, among 5886 individuals who had undergone CR after an acute MI, the lowest mortality and hospitalization rates as long as the fewest emergency room visits in the completers versus non completers. Furthermore, a strong dose–response relationship has also been demonstrated between the number of CR sessions and long-term outcomes with a lower risks of death and MI at 4 years.[17]

Even though maximal benefit of CR derives from early initiation of exercise (as early as 1 week after MI hospital discharge),[18] the rehabilitative programmes often begin late after the acute event (more than one month). Furthermore, most of the studies available in the literature regarding an early beginning of a structured physical activity after an acute MI were conducted in low risk cohorts and in outpatient settings. [19-20]

This study aimed to evaluate, safety, efficacy and impact on short and long term prognosis of an early, in-hospital, exercised based CR, after an acute MI in a selected high risk population.

METHODS

Study design. In the period 2008-2012, 376 consecutive patients (mean age 64.4±12.3 years, male 77%) after an acute MI (ST elevation 63%) were directly transferred from the University Hospital of Padua to our Prevention and Rehabilitation Unit in Cortina d'Ampezzo (BL) for a structured, intensive, CR programme. Patients were selected by the submitting centre according to the risk profile: low risk patients followed an out-patient CR programme in another centre and were excluded from this study. All patients had an angiography-documented CAD and the vast majority (84.8%) received a percutaneous treatment of at least one vessel. Those patients who underwent coronary artery bypass grafting and those with echo- or MRI-documented intracavitary thrombosis, extreme thinning or rupture of the ventricular wall and/or intra-myocardial bleeding were excluded. In the present study population risk profile was medium-high: 87% patients had a complicated MI (cardiogenic shock or pulmonary edema, cardiac arrest, complex ventricular arrhythmias), 47% had an incomplete revascularization because of operator decision, coronary anatomy or technical failure) and the mean length stay in the submitting Hospital before transfer to CR unit was extremely long (16,4±9,9 days); at the beginning of the programme, the majority of patients (84%) was in NYHA functional class II or III. Demography, medical history and conventional risk factors, physical examination and treatment data were recorded for all the patients; routine biochemical analyses and a 2-D echocardiogram were obtained as well. In order to evaluate the effects of a depressed left ventricular ejection fraction (EF) on the rehabilitative process, the patients were divided into 2 groups according to a 40% EF cut-off at enrollment. Functional capacity was assessed by a six-minute walking test (6MWT) on admission and at discharge and by a cardiopulmonary exercise test (CPET).

The study was approved by the local institutional review board, and a standard informed consent to 6MWT and CPET was obtained from all patients.

Rehabilitation programme. The training protocol consisted of a low/medium intensity exercise protocol developed in 3 sets of exercises, 6 days a week: 30 min of respiratory workout, followed by an aerobic session on a cyclette (or on an arm-ergometer in those patients who were not able to cycle) in the morning and, in the afternoon, 30 min of *callisthenic* exercises. Each session was supervised by a physician and a physiotherapist and all patients were ECG monitored by a telemetry system. Aerobic training was performed using a constant work rate modality without exceeding 70% of the maximal predicted peak heart rate (HR) for each patient.[21] Each aerobic session lasted 10 minutes at the beginning, with a 5 minutes progressive increase to reach a 30 min target; the exercise prescription and evaluation of exercise intensity was carefully derived from the subjective rating of perceived exertion, using a category ratio Borg scale. [21] Individual and group counseling meetings, psychological and nutritional evaluation were also performed for all patients.

Six minute walking test. The 6MWT was performed in a 30 m long, unobstructed indoor corridor, according to the American Thoracic Society recommendations,[22] on admission and then repeated on the day of discharge.

Cardiopulmonary exercise test. The CPET was performed at the end of the rehabilitative period on a computer-driven cycle ergometer (*Cardiovit CS-200 Ergo-Spiro, Schiller AG, Baar, CH ; Ergoselect 100 ergometer, Ergoline GmbH, Bitz, D*). A progressive ramp protocol of 6 to 10 W/min was used, until subjective exhaustion or appearance of clinical or electrocardiographic criteria for termination.[23] Expired gas was collected by means of a tightly fitting face mask and continuously analyzed during the exercise test (*Schiller Ganshor CS-200 Power Cube*). Peak oxygen consumption (peak-VO_2) was expressed relative to body weight. The peak exercise capacity was expressed in Watt as maximum sustained workload (W-max). The anaerobic threshold was determined non invasively using a dual-method approach (both the ventilatory equivalents and the V-slope methods). The peak respiratory exchange ratio was calculated as VCO_2/VO_2 at the peak of the exercise.[24]

Follow up. It was obtained by means of a telephonic interview made by a physician. Eleven patients (2.9%) were lost, so the follow up was conducted on 365 subjects. The first end-points were all-cause mortality, cardiac mortality and major adverse cardiovascular events (MACE) (death, new MI, new revascularization, heart failure or stroke). Secondary end-points were adherence to therapy and life-style changes (smoking cessation and physical activity).

Statistical analysis. Continuous variables were expressed as mean ± standard deviation and compared between groups using an unpaired t-test. The majority of the variables were approximately normally distributed (Kolmogorov-Smirnov and Shapiro Wilk tests for data normality were used). Log transformations for several variables were considered but did not change the conclusions. Thus, all results presented are based on untransformed data. Categorical variables were expressed as frequencies and proportions and were compared between groups by the chi-squared test. The relationships between continuous variables were evaluated by Pearson’s correlation coefficient. Survival curves were calculated by the Kaplan-Meier method and groups were compared with a long-rank test. A Cox regression multivariate analysis was performed as well to determine the influence of different factors (age>65 years, EF<40%, known diabetes, ST elevation MI, chronic renal failure, atrial fibrillation, left bundle branch block) on all cause mortality. All reported probability values are two-tailed and the significance level was set at 0.05. Statistical analyses were performed using SPSS 18 software package (SPSS Inc, Chicago, IL,USA).

RESULTS

Clinical characteristics (table 1). Comparison between the two groups (EF<40% vs EF>40%) showed no significant differences in terms of age, sex, length of stay in the rehabilitative unit, rate of smokers, rate of incomplete revascularization and prevalence of metabolic syndrome. Lower EF group patients had a significantly higher incidence of a previous MI (25.3% vs 16.1%, p = 0.04) and lower incidence of STEMI (51% vs 67%, p <0.01, higher prevalence of diabetes (36.4% vs 20.3%, p = 0.01) and greater degree of anemia (Hb 11.50±1.60 vs 12.40±1.49, p<0.01. In addition, they stayed longer in the acute Hospital than the other group (20.7 ± 12.7 days vs 14.9 ± 8.6 days, p <0.01).

In the whole population, no fatal events occurred during the CR stay (14.6±3.1 days) and only 4 patients (1,06%) dropped out of the programme due to non-fatal complications: 2 cases of instable, refractory angina and 2 cases of persistent arrhythmias (1 complete AV block and 1 non-sustained ventricular tachycardia).

At the end of the CR programme almost all subjects were on aspirin, statins, beta-blockers and ACE inhibitors, without significant differences between the groups according to EF.

Exercise capacity

Change in six-minute walking test (table 2). All patients improved their functional status at the end of the rehabilitative period. Compared with baseline, a significant increase in the six minute walk distance at discharge was observed (Δ6MWT in the entire population: 70.7±55.7 m, p<0.05).

Patients with EF <40%, despite the shorter distance walked, both at entry and at discharge, showed a similar degree of functional recovery when compared to the subjects with EF>40% (Δ-6MWT respectively 65.9±62.9 m vs 72.2±53.2 m, p=ns).

Cardiopulmonary Exercise Test (table 2). CPET was performed at discharge in 95% of the entire population. Exercise capacity was significantly poorer in the subjects with EF <40% compared to those with EF> 40%. As expected, patients with a lower EF achieved a lower maximal workload, rate-pressure product and oxygen consumption both at peak exercise and at the anaerobic threshold; the VE/VCO_2 slope was higher in the EF<40% as well.

A correlation between VO_2 at peak exercise at CPET and the distance walked in 6 minutes at discharge was found (R^2 =0.43, p<0.01).

Outcome

Behavioral habits. Active smoking habit at the time of the MI was recorded in 32.1%. Among these subjects, 77% had definitively given up smoking at follow up. In the whole population, 73% referred to continue a regular physical activity (at least 3 aerobic exercise sessions per week, of 30 min each). This group showed a lower rate of MACE when compared to sedentary subjects (10.8% vs 22.8%, p 0.02), although the mean age was not different between the two groups (63.76±12.4 years vs 62.0±12.4 years, p=ns).

Adherence to therapy (table 1). At the follow-up, an high adherence to therapy was registered (aspirin: 96.4%; betablockers: 85.2%; statins: 95.6%; ACE-I/ AT II antagonists: 89.0%).

Mortality and major cardiovascular events (table 3, fig 1). In the whole population cardiac mortality and all cause mortality resulted 5.0% and 8.0 % respectively at 1 year and 8.0 % and 13.0 % at 5 years. As expected, the prognosis was worse in older people and in the lower EF group; effectively, in these subjects the incidence of MACE was higher.

Cox regression multivariate analysis showed that age>65 years, (regression coefficient B=-0.64, p=0.03), EF<40% (B= 0.86, p<0.01) and known diabetes (B= -0.73, p=0.01) were significant independent negative prognostic predictors.

DISCUSSION

To our knowledge, this is the first study that investigate, in a real world setting, the safety and efficacy of an early (within 2 weeks from the event) and intensive (in Hospital, 3 sessions daily, 6 days for week) exercise-based CR in high risk patients after a MI. Safety was demonstrated by the low drop out rate (only 1,06%) and the absence of major complications during the CR stay, notwithstanding the compromised clinical conditions at enrollment. Efficacy was demonstrated by a noteworthy increase on functional capacity in the short term, apart from the residual ventricular function, as well as a high adherence to therapy and to the proposed lifestyle modifications at follow up. This may have produced a positive effect on mortality in the long term (quite low considering the high risk profile of the population).

Safety of an early aerobic training after a MI

The safety of a structured exercise training is widely documented in CAD patients, when the exercise programme, mostly extensive, starts at least 1 month after the acute event. Vongvanich P. et al.[25] registered four non-fatal major events (3 cardiac arrests and 1 AMI), in a period of nine years with only one serious complication every 67.126 exercise hours per patient. More recently Pavy and colleagues,[26] analyzing data from 65 cardiac rehabilitation centers in France, confirmed the low rate of major cardiovascular events during rehabilitation: 1 event every 8484 stress tests or every 49.565 exercise hours and 1.3 cardiac arrests per million exercise hours.

Very little is still known about the safety of an aerobic training initiated soon after an acute coronary event. In 1982 Sivarajan et al.[19] demonstrated the safety and efficacy of an exercise programme started shortly after a MI (mean 4.5 days) and maintained for 3 months, on 135 patients compared with a control group (61 patients) that received conventional medical management. However, patients who were older than 70 years or who had a complicated MI were excluded from the study. More recently, Aamont et al.[20] have evaluated the effect of an early start in exercise training in low risk patients after an uncomplicated MI (14 days after the event) compared with a delayed start control group (4 weeks after the event). This randomized study included a small number of patients: 20 subjects in the first group (60.9±10.8 years) and 19 in the second (57.7±9.2 years). Exercise training was completed without complications by all participants and the CPET showed an improved functional capacity in all groups after CR, without differences between them.

Our study shows that a structured, in-hospital, exercise training conducted under strict cardiological surveillance without delay after clinical stabilization, with a progressive intensity increase, it's safe also in high risk patients after a complicated MI.

Efficacy

Beneficial effects of an exercise based CR on functional capacity is clearly documented in CAD patients.[27-29] In our study, at the end of the 2 weeks rehabilitative period, all patients increased the distance walked (mean 6MWT gain 70.67±55.7 m, $p<0.05$). Other authors[30] reported similar results but in younger and lower risk population, after an extensive CR programme of at least 8 weeks.

Importantly, in our study functional recovery was independent from the EF; in fact patients with an EF<40% despite worse clinical characteristics - (major rate of diabetes and comorbidities) and a minor absolute functional capacity as measured at CPET – showed a functional recovery similar to that of patients with EF>40%.

The 6MWT is a submaximal test, reproducible, safe, inexpensive and reflective of daily life activities; it can be performed by the majority of patients and is widely used for the assessment of the functional status in CR.[31,32] Our data confirmed the known correlation between the distance walked in the 6MWT and the VO2 achieved at the peak of the exercise during the cycle ergometer test.[33,34]

Comprehensive risk factors management: smoking cessation and physical activity

The most important aim of a comprehensive CR is to positively modify the risk factors cluster, in particular smoking and physical inactivity.[12,35]

In worldwide clinical records, the rate of smokers that quit after an acute MI is variable from 28% to 75%.[36,37] In our analysis, the rate of smoke cessation was 77% at follow up. This data confirms the importance of frequent and incisive counseling interventions carried out by qualified professionals, supported by psychologists and supplemented by teaching materials.[38] However, part of the advantage must be attributed to the special educational intervention timing (immediately post MA), characterized by the patient's predisposition to a lifestyle change, combined with the impossibility of smoking during the hospitalization.

Seventy per cent of our patients confirmed to continue a regular aerobic activity for at least 30 minutes, 3 times a week. Physically active patients had a smaller percentage of MACE when compared to non- or less-active patients (10.8% vs 22.6%, p=0.02), independently of age.

Adherence to therapy

The data in the literature regarding the adherence to prescribed therapy (aspirin, beta-blockers, ACE-I/ARB-II and statins) after a MI are discouraging. Approximately 20-50% of patients does not adhere to the chronic therapy and the drug suspension is especially elevated in the first month, with a serious impact on survival.[39,40]

In our study more than 90% of patients continued to take the prescribed drug after 5 years. The adherence depends on a lot of factors, among which the doctor-patient relationship plays a crucial role; health professionals lack of time often represents an obstacle to the realization of the indispensable "therapeutic alliance" between patients and care givers. Thus a comprehensive CR may play a fundamental role reinforcing the therapeutic suggestions provided during the acute phase of the disease.[41]

Survival

Favourable effects of CR on prognosis after a MI have been established.[27,42] This could be in part explained, besides the life-style interventions, by the positive effect of physical activity on ventricular remodeling and the residual left ventricular EF.[43,44] A recent meta-analysis by Haykowsky et al.[45] on 1029 clinical trials confirmed that exercise training has beneficial effects on LV remodeling in clinically stable post-MI patients, with the greatest benefits in an increase of EF and decrease of end-systolic and end-diastolic volume.

A recent Italian survey considering patients discharged from the intensive care units after an acute MI, reported an all cause mortality at 30-day of 5.6% and 3.4% for ST elevation MI and non ST elevation MI patients, respectively.[3] In the U.S.A, Coles et al.,[6] on post acute unselected MI patients, reported in 2007 an all-cause death rates of 8.9%, 16.4%, and 23.4%, at 3-month, 1-year, and 2-year respectively, suggesting the opportunity to enhance post-discharge management practices. Although it's difficult to compare populations with different clinical features and treated with different methods, all-cause mortality and cardiac mortality in our study were quite low, particularly considering the high risk profile of the population.

Study limitations

This is an observational single centre, not randomized, study. Since nowadays CR is considered a class I recommendation, patient randomization could be difficult and also not appropriate for ethical reasons.

The study was conducted in an in-hospital setting, where the patients begun the rehabilitative interventions early after the acute event and followed a relatively short period of intensive, exercise-based CR, under strict surveillance of a team including a physician. This kind of programme is somehow uncommon in Europe and in USA, where the majority of the patients follow longer-term, lower-intensity, outpatient rehabilitation, often monitored only by a team of physiotherapists. Whether the results of this study are applicable to these programmes is unknown. Furthermore, the optimal type of training, as well as the optimal training frequency and intensity need further investigation in the future.

Conclusions: An early and intensive CR, based on physical activity and counseling, resulted to be safe and effective in high risk patients after an acute MI, both in the short and in the long-period. As a matter of fact, a significant increase on functional capacity in the short term - apart from the residual ventricular function - and a high adherence to therapy and to the proposed lifestyle modifications was achieved. Despite the high risk profile, this may have produced a positive effect on mortality in the long term.

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Table 1. Clinical features

	EF < 40 n=99	**EF > 40** n=277	**All** n=376	**p**
Clinical characteristics				
Age (yrs)	66.1±11.6	63.7±12.5	64.4±12.3	0.11
Male sex (%)	78.8	76.9	77.4	0.69
STEMI (%)	51.0	67.1	62.7	<0.01
Vessels (critical lesion)	2.2±0.8	2.0±0.9	2.1±0.9	0.09
Vessels treated	1.2±0.9	1.3±0.8	1.3±0.8	0.20
Incomplete revascularization (%)	52.5	44.4	46.5	0.16
Hypertension (%)	79.8	75.3	76.5	0.38
Diabetes (%)	43.4	23.0	28.2	<0.01
Pre-diabetes (%)	30.1	42.0	39.0	0.06
Metabolic Syndrome (%)	72.7	69.4	70.3	0.56
Previous MI (%)	25.3	16.1	18.5	0.04
Previous PTCA (%)	14.3	13.9	14.0	0.91
Previous CABG (%)	12.1	6.9	8.3	0.10
Vascular disease (%)	21.2	6.5	10.4	<0.01
Pulmonary disease (%)	10.1	3.7	5.4	0.01
Renal Failure (%)	14.1	5.9	8.1	0.01
Atrial Fibrillation (%)	9.1	5.1	6.2	0.16
Current smoker at MI onset (%)	33.3	31.7	32.1	0.77
NYHA class II/III (%)	45.5/47.5	53.3/22.3	51.2/29.0	<0.01
EF (%)	33.8±4.9	51.7±6.9	47.0±10.2	<0.01
BMI (kg/m^2)	27.2±5.5	27.4±4.3	27.4±4.6	0.69
Haemoglobin at entry (g/dL)	11.5±1.6	12.4±1.5	12.2±1.6	<0.01
Stay in CR (days)	15.2±3.1	14.4±3.1	14.6±3.1	0.03
Time to rehab (days)	20.7±12.7	14.9±8.6	16.4±9.9	<0.01
Drop out (n) (%)	0 (0.0)	4 (1.4)	4 (1.0)	0.23
Medication (%)				
Aspirin	98.9	97.8	98.1/96.4*	0.48
Clopidogrel	90.4	96.0	94.6	0.04
ß-blockers	89.4	89.0	89.1/85.2*	0.92
ACE-I	78.7	83.9	82.6/71.3*	0.26
AT-II ant	14.9	11.7	12.5/16.4*	0.42
Statins	98.9	97.8	98.1/95.6*	0.49

Values expressed as n (%) or mean ± SD. *(At discharge/follow up)
EF=Left ventricular ejection fraction; STEMI=ST elevation myocardial infarction; MI=myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft; NYHA= New York Heart Association; BMI= body mass index; ACE-I = angiotensin-converting enzyme inhibitor; AT-II ant = angiotensin II receptor antagonist. Renal failure= at least moderate reduction in glomerular filtration rate (30-59 ml/min/1.73 m2)

Table 2. Functional status assessment

	EF < 40 n=99	EF > 40 n=277	All n=376	p
6MWT				
Basal (mt)	356.5±135.7	424.2±122.5	407.5±129.1	< 0.01
Pre-discharge (mt)	411.3±134.0	491.3±122.1	471.3±129.7	<0.01
Δ6MWT (mt)	65.9±62.9	72.2±53.2	70.7±55.7	0.37
CPET (n/tot) (%)	88/99 (88)	269/277 (97)	357/376 (95)	
Max workload (W)	62.7±22.3	83.1±31.2	78.2±30.6	<0.01
Peak-VO_2 (ml/Kg/min)	15.2±3.9	18.2±5.2	17.5±5.1	<0.01
Peak-VO_2 (% predicted)	62.6±18.2	72.2±18.8	69.9±19.1	<0.01
HR max (beat/min)	107.6±16.8	109.2±18.7	108.8±18.2	0.52
HR max (% predicted)	70.3±10.4	69.1±10.6	69.4±10.6	0.38
RPP (mmHg·beat/min)	14664±4208	16777±4698	16265±4666	<0.01
AT HR (beat/min)	94.5±12.5	90.7±14.7	91.6±14.3	0.05
AT VO_2 (ml/Kg/min)	12.1±2.5	14.0±6.3	13.5±5.6	0.02
RER max	1.1±0.1	1.1±0.1	1.1±0.1	0.77
VE/VCO_2 slope	28.8±4.9	26.3±4.4	26.8±4.6	<0.01

Values expressed as mean ± SD.
6MWT= six minute walking test; Δ6MWT= change in the 6 min walking test (mean calculated only in those patients who performed both the baseline and pre-discharge test); CPET= cardiopulmonary exercise testing; Peak-VO_2= peak O_2 consumption; HR max= maximal heart rate; AT HR= anaerobic threshold heart rate; RPP= rate-pressure product; AT VO_2= anaerobic threshold O_2 consumption; RER max= maximal respiratory exchange ratio; VE/VCO_2 slope= minute ventilation/carbon dioxide output slope.

Table 3. Events at follow up according to residual EF and age (unadjusted data)

Events (n) (%)	EF < 40 n=95	EF > 40 n=270	Age > 65 n=177	Age < 65 n=188	All n=365	p*	p±
All-cause death	15 (15.8)	13 (4.8)	25 (14.1)	3 (1.6)	28 (7.7)	0.01	<0.01
Cardiac death	13 (13.7)	5 (1.9)	15 (8.5)	3 (1.6)	18 (4.9)	<0.01	0.02
MACE	30 (31.6)	42 (15.6)	46 (26.0)	26 (13.8)	72 (19.7)	0.01	0.04
Myocardial infarction	2 (2.5)	7 (2.7)	8 (5.3)	1 (0.5)	9 (2.7)	0.91	0.07
PTCA/CABG	3 (3.8)	18 (7.0)	11 (7.2)	10 (5.4)	21 (6.2)	0.29	0.48
Heart Failure	13 (16.3)	12 (4.7)	13 (8.6)	12 (6.5)	25 (7.4)	0.01	0.47
Stroke	1 (1.3)	6 (2.3)	6 (3.9)	1 (0.5)	7 (2.1)	0.55	0.03

* p between EF groups; ± p between age groups; MACE=Major Adverse Cardiac Events (Cardiac mortality, re-infarction, new PTCA/CABG, heart failure, stroke); EF=Left ventricular ejection fraction; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft

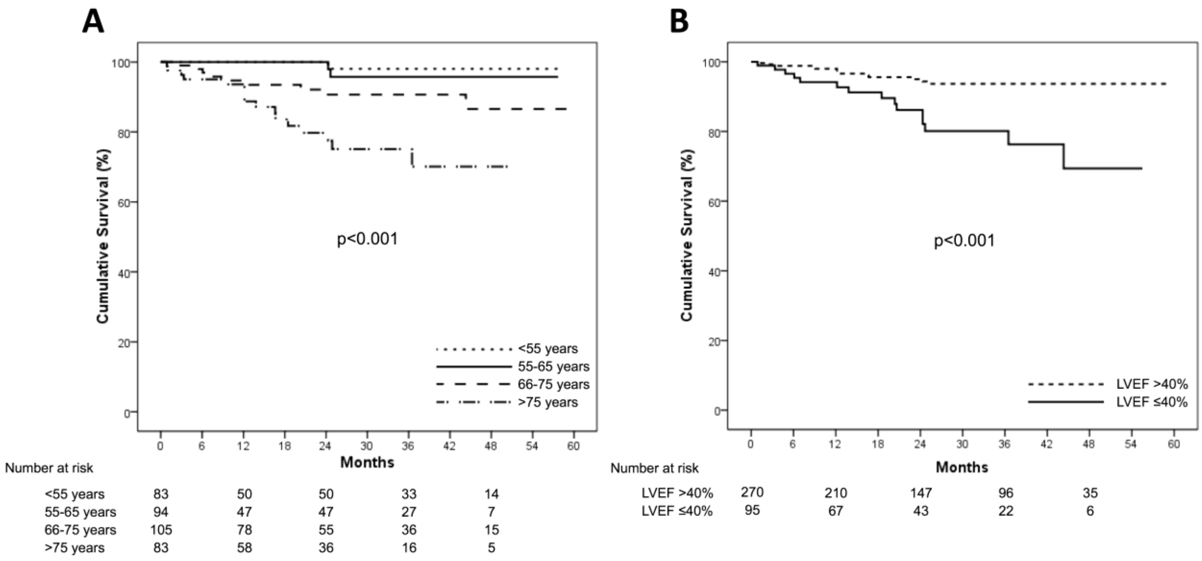

Fig. 1. All cause-mortality according to age groups (A) and left ventricular ejection fraction (B).