Cardiac rehabilitation in very old patients: impact of baseline functional capacity on treatment effectiveness

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Abstract

Background: Randomized and observational studies demonstrate that cardiac rehabilitation (CR) is effective in promoting functional recovery and adherence to secondary cardiovascular prevention. There is a paucity of data on the efficacy of CR in elderly. We verified the effectiveness of CR in a very old population after cardiac events and identified independent predictors of improvement in functional capacity.

Methods: We evaluated all patients aged ≥75 years, referred to our outpatient Cardiac Rehabilitation Unit with one of the following causes: acute coronary syndrome, cardiac artery by-pass grafting or heart valve replacement/repair procedures. All enrolled patients attended a four week supervised training program; and were evaluated at admission and at discharge with VO2peak (Cardiopulmonary stress test), distance walked (6-Minute Walking test) and Torque peak (isokinetic dynamometer).

Results: We enrolled 160 patients (mean age 80±4 years), the mean value of the three indexes of physical performance considered (power, resistance, strength) improved from baseline to discharge: VO2peak +10.9%; distance walked +11.0%; Torque peak +11.5%. Performance at admission emerged as an independent predictor **of improvement of 15% in all three indexes: baseline VO2 peak OR =0.86 (95% IC=0.77-0.97); baseline 6WT OR= 0.99 (95% IC=0.99-1.00); baseline PT 90° OR=0.96 (95% IC=0.94-0.98). The higher the performance level at the admission, the lower the improvement at discharge.**

Conclusion: In very old cardiac outpatient CR program is effective to improve exercise tolerance and muscle strength. In addiction our data seem to suggest the presence of basal ceiling values of exercise tolerance and muscle strength, above which it is unlikely to expect a significant improvement.

Introduction

Cardiovascular diseases, with coronary heart disease alone accounting for more than half of all cardiovascular deaths, are the leading cause of death in industrialized countries (1). Their prevalence rises exponentially with age and peaks to more than 70% among persons aged 75 years or more. A similar pattern is observed for the incidence of first myocardial infarction (1).

Over the last two decades, the remarkably improved management of acute cardiovascular events has reduced heart diseas mortality (2), but at the cost of an increase in the burden of disability (3).

Randomized clinical trials, meta-analyses, and observational studies have demonstrated that structured cardiac rehabilitation (CR) is highly effective in improving functional recovery and exercise tolerance, and adherence to secondary prevention measures recommended by guidelines as well (4).

Ideally, physical exercise training in a CR program should produce sizable improvements in cardio-circulatory and skeletal muscles performance, at no harm of untoward events, with the issue of safety being particularly relevant in older, frail individuals.

Updated guidelines precisely define the core components and outcome measures of CR that is considered, for patients with cardiovascular diseases, as an integral part of long-term secondary prevention programs (5, 6), in which baseline assessment is essential to design an individually tailored training. Accordingly, the response to baseline, symptom-limited exercise stress test has to be used as a starting point to calculate the individual training workload.

Despite results of a randomized trial (7) suggest that, compared to younger patients, those older than 75 years obtain similar, or even larger, improvements in exercise tolerance and self-reported physical function from exercise-based CR, the mean age of patients enrolled in most studies of CR is largely less than 75 years (8).

Moreover, the limited available data indicate that CR might reduce the risk of functional and cognitive decline and enhance the probability of global functional recovery, thereby preserving the independence in activities of daily living (9).

Given the paucity of evidence of CR in older persons, the present observational study was conducted in patients older than 75 years with a recent cardiac event, to assess the efficacy of a CR program in terms of exercise tolerance and muscle strength improvement, and to identify the independent predictors of changes in functional capacity from baseline.

Methods

All consecutive patients aged 75 years or more, referred to the CR Unit of Careggi University Hospital between 2007 and 2010, after an acute coronary syndrome (ACS) treated or not with percutaneous coronary angioplasty, or coronary artery by-pass grafting (CABG) and/or surgical valve replacement/repair procedures, **were considered to enter in our CR a program**.

Criteria for exclusion from our study were: significant cognitive impairment (Mini Mental State Examination score <18 (10) or disability in two or more of Katz BADL (11); significant musculoskeletal disease or any absolute or relative contraindication to exercise stress test (12); any disease with expected negative prognosis within 6 months; heart failure diagnosed according to ESC criteria (13), left ventricular ejection fraction (LVEF) ≤35% .

~~**Patients not admitted to standard CR program because of exclusion criteria were offered an ad-hoc, personalized CR program and attended periodical meetings focused on secondary cardiovascular prevention; in particular, those with heart failure were admitted to exercise sessions and educational programs specifically designed by a skilled physiotherapists.**~~

The present study has been approved by Local Ethic Committee and it complies with the rules of the declaration of Helsinki. The study is also registered at ClinicalTrial.gov with n°NCT0064113.

General evaluation: At baseline, each patient received a comprehensive clinical and geriatric evaluation, including: demographics; social and medical history; **we consider sedentary patients who perform less than 20 minutes of walk at a normal pace 3 times a week (14).** Assessment of comorbidity by the Charlson-Age Comorbidity Index **(score: 0-43)** (15) of global functional status by Basic Activities of Daily Living **(preserved BADL 0-6/6)** and Instrumental Activities of Daily Living **(preserved IADL 0-8/8)** (16) scales, and of depressive symptoms by the 15-item Geriatric Depression Scale (GDS) **(score: 0-15)** (17), drug therapy. a 12-lead ECG and a mono- and two-dimensional echocardiogram.

Cardiopulmonary and muscular performance tests: at baseline and at the end of physical training that was an integral component of the CR program, each patient was evaluated with the following tests:

- *Cardiopulmonary stress test:* **it was performed at cycle ergometry** (Formula ESAOTE® Biomedica instrument) with a progressive incremental 10 watt/min protocol associated with "breath to breath" oxygen consumption analysis (CPX Medical Graphics system®). The outcome measure was the O_2 consumption at peak exercise (VO_2peak, ml/kg/min).
- ***Six minute walking test**:* the test was conducted according to the Guyatt protocol in a 30-meter corridor (18) with telemetric-ECG and O_2 saturation monitoring, without previous familiarization test. The outcome measure was total distance walked (in meters).
- *Isokinetic muscle strength***:** the test was performed with isokinetic dynamometer (BIODEX Medical System®) with three progressive angular speed (5 repeats at 90°/sec; 8 repeats at 120°/sec; 10 repeats at 180°/sec), evaluating the quadriceps and hamstring muscles strength, in flexion-extension of both inferior limbs. The outcome measure was the 90°Torque peak (Newton for meter) (19).

Exercise training program: All patients attended a 4-weeks of aerobic training program in the Day-Hospital of the CR Unit five days/week, setting the intensity at 60-70% of VO_2peak attained at baseline cardiopulmonary stress test. **The CR program was individually tailored and physical activity intensity changed weekly by using the Borg Rating of Perceived Exertion Scale (20), maintaining an intensity of 11–13. This program reflects the routinely length of rehabilitation provided for the national health care system.**

Training sessions consisted of 30-minute sessions of either biking or callisthenic exercises, on alternate days. **The callisthenic program was structured by a warming period followed by a sequence of 8 exercises (2 minutes each one followed by 1 minute at rest), with the aim to ameliorate the strength of the leg and stretching the muscles of the trunk, to achieve a better**

autonomy in daily activities. The progressive improvement of resistance was obtained applying ankle or wrist bands of progressive weight (0.5 kg , 1 kg) on the basis of Borg Rating of Perceived Exertion Scale, re-evaluated weekly. All activities were performed under the supervision of an expert physiotherapist, with telemetric ECG and non-invasive arterial pressure monitoring.

During the CR program, patients and selected family members received formal courses on the management of cardiac risk and emotional profile by physicians, physiotherapists, nurses, a dietician and a psychologist.

Statistical analysis: All statistical analyses were performed with SPSS® v.18.0 statistical package. Continuous and categorical variables are given as mean ± standard or percentages, respectively. Univariate analysis, using Pearson R statistics or Chi-square test, was used to test associations of demographic, clinical and echocardiographic variables with exercise and muscle strength performance indexes at the end of the CR. Significantly associated variables were then entered into multivariable logistic models, to identify the independent predictors of CR program effectiveness. To this purpose, the clinical effectiveness of the CR program was defined by two approaches: first, by verifying the presence of improvement in the exercise performance tests from baseline to final evaluation; second, by evaluating the independent predictors of the excellent or poor physical performance improvement defined respectively as a modification >15% or ≤ 5% in the exercise and muscle strength respect to basal performance.

A p value <0.05 was considered statistically significant.

Results

***Study population:* 236 patients aged ≥ 75 yrs (66.5% males mean age 81±4 yrs) were consecutively evaluated to start our usual CR program. Of these, 39 did not attend to CR program: for personal decision (n=8), for logistic or social barriers (n=12), for clinical instability or recurring hospitalization (n=16), or severe comorbidity (n=3). Other 37 started our CR program but they were not eligible for the present study because they met predefined exclusion criteria (LVEF ≤ 35%: n=23; severe cognitive impairment: n=9; severe muscular-skeletal disease: n=5).**

Finally, the study population included 160 patients (67,8% of those initially screened; 70.6% males; mean age was 80±4 years). Recent ACS accounted for the vast majority (78.1%) of cases, followed by recent CABG (15%), and cardiac valve replacement/repair (6.9%). The mean time delay between acute hospital discharge and admission to CR program was 12 ± 10 days.

Patients did not show significant disability as demonstrated by mean level of BADL (5.8+/- 0.6) and IADL (7.2+/- 1.4) or cognitive impairment (MMSE score 27.8+/-2.1).

The clinical characteristics of the study population are reported in Table 1. The average Charlson-Age Comorbidity Index score indicated at least moderate comorbidity. Most patients were married, with a low formal education. At baseline, over 80% of patients were receiving all four classes of drugs recommended for ischemic heart disease (antiplatelets, ACE/ARB, beta-blockers and statins).

The mean number of exercise sessions performed in a 4 week program was 17±3; 90% of patients performed >80% of sessions.

Safety: Our structured CR program proved to be safe; in fact, despite the occurrence of some medical complication, all 160 patients could completed the program. CR-related complications included 3 episodes of chest pain during exercise (treated by potentiating medical therapy), 1 hypertensive crisis during exercise, 1 paroxysmal supraventricular tachycardia during exercise, 2 falls without consequences. Other medical events during the program included 3 bronchopneumonias, 1 muscular hematoma, 1 transient ischemic attack, 1 worsening of renal function resolved by interruption of ACE-I therapy, 2 episodes of gastrointestinal bleeding requiring hospitalization (but not transfusion of red blood cells) with interruption of CR for less than 10 days.

Efficacy: In the study population as a whole, all three indexes of physical performance (aerobic capacity, resistance, muscular strength) improved significantly from baseline to the end of CR program: VO_2peak improved from 13.9±3.7 at the entry to 15.1±4.1 ml/kg/min, ($p<0.001$) with an overall increment of 10.9 % ; the distance walked from 397.7±93.3 to 433.8±92.1 meters, ($p<0.001$) with an overall increment of 11.0 %.and the muscular strength from 62.2±23.3 to 71.4±25.2 Newton for meter, ($p<0.001$) with an overall increment of 11.5 %. Of note, an improvement > 5% in VO2peak, distance walked and 90°Torque peak at the end of CR program has been reached respectively in 57.8%, 62.5% and 73.6% .

In the Figure we reported the relationship between increment in final performance index defined poor (≤5%) or excellent (>15%) of the three indexes respect to basal value at the entry in the program. We can notice that patients with poor incremental performance results at the end of the CR program had a significant higher mean value at the entry for all the three indexes and, symmetrically, patients with an excellent improvement after CR program presented a significant lower values in all the three indexes at the entry.

Predictors of improvement in exercise tolerance and muscle strength: The univariable associations of socio-demographic and clinical variables with the two cut-off (≤5% vs. >5%; ≤15% vs. >15%) changes in indicators of exercise tolerance and muscle strength from baseline to the end of CR program were systematically explored **as reported in Tables 2 and 3**.

A marginally lower use of statins was found among those who increased VO_2peak by ≤5% Compared to patients who improved by ≤15%, those who improved the 6WT by >15% were more frequently females, with more prevalent depressive symptoms at baseline and sedentary lifestyle prior to acute event, and less frequently diabetics; furthermore, a >15% increase in Torque peak at 90° was associated with lower Charlson index, greater BADL score and lower BMI.

None of the other socio-demographic and clinical variables were statistically associated with the exercise tolerance and muscle strength improvement, marital status and education level included (data not reported in the tables).

The multivariable predictors of a "poor" ($\leq$5%) or an "excellent" (>15%) response to the program are reported in Table 4, in different models calculated for each performance index. In all models, a higher baseline value was the single strongest predictor of a poor response and, conversely, a lower baseline value the strongest predictor of an excellent response for each performance index; increasing age was a significantly negative predictor of a poor response for VO_2peak and 6WT, use of statins a predictor of a poor response for VO_2peak only, while higher Charlson index and BMI and higher BADL score were respectively negative and positive predictors of an excellent response for Torque peak at 90°.

Discussion

Despite evidence of clinical and functional efficacy, referral to CR and secondary prevention programs remains very low, particularly among older compared to middle-aged clinical populations (8).

Thus, the first interesting result of this observational study is the high proportion (more than 67%) of patients enrolled in the selected cohort of older (75+ years of age) individuals referred as candidates to outpatient CR program. A broad spectrum of factors and processes influence the rate of attendance to CR program, ranging from clinical and social factors to health professional advice (21). In fact, recent data underlined the importance of early interventions to increase patient attendance, demonstrating that an early appointment significantly improve attendance to CR (20): in particular, an early (≤ 10 days) appointment significantly increases the initial participation to CR (22). In our study, the mean time-lapse between hospital discharge to first assessment visit prior to entry in the CR program was 12 days.

A second valuable observation is the remarkably low rate of adverse events in our very old study population: indeed, no patient interrupted had to be withdrawn permanently from, nor severe cardiac or non cardiac complications **requiring hospitalization** occurred and, when necessary, the interruption period for any clinical reasons was less than 10 days. Therefore, our results strongly support the belief that structured CR program is safe even for very old patients.

Third, as a main result of the study, we observed a significant average enhancement of exercise capacity and muscular strength in very old patients at the end of the CR program: almost 60% of the study population improved by more than 5% in all the three performance indexes from baseline, and remarkable proportion improved by more than 15% **after 4-weeks of intervention**. **We considered our result as a significant, whereas Ades and Coll. (23) obtained a 17% of peak aerobic capacity increase after 3 months in a population mainly composed by patients with mean age 61±11 years. Our findings are consistent with those obtained by the Researchers of German**

Sport University of Cologne (24) that demonstrated an increment of 13.5% and 16.2 % in distance walked at Six minute walking test and VO2 peak respectively in elderly patients after cardiac surgery at the end of usual CR exercise 3-weeks program.

In our opinion, this finding is of crucial relevance from geriatric perspective, as a significant increase in global functional capacity has been reported to reduce the risk of incident disability, and improve health related quality of life, social reintegration and independence (25).

The significant benefit in terms of exercise tolerance, endurance and muscle strength that we obtained in a population with a mean age of 80 years is consistent with recent data (24), which demonstrated an improvement in functional capacity over time after CABG in those participants aged 80 and older in whom routine CR was integrated with resistance and balance training.

As reported in our multivariable analysis, the strongest predictor of poor or excellent improvement at the end of CR was the baseline result of all three performance tests: the lower the baseline values, the higher the increase in functional capacity at the end of the CR program. For VO_2peak, this result had already been pointed out by Eder et al. (26) but, to our knowledge, no similar data had been published for the two other performance indexes that represent clinically valuable outcomes of CR.

Interestingly, the use of statin negatively predicted the VO_2peak increase at the end of CR program. As reported in Table 2, statins therapy is associated with a 3-fold risk of not reaching a significant improvement at the end of CR program. This results is consistent with recent evidence that simvastatin attenuates the increase in cardio-respiratory fitness and skeletal muscle mitochondrial content in response to exercise training in overweight patients at risk of metabolic syndrome (27); **differently Rengo et al. (28) did not find any detrimental effect of statin on exercise training response in a large cohort of middle-aged cardiac patients.**

The pathophysiological mechanisms involved in this negative effect of statin seem to be related to a detrimental effect in mitochondrial function, to glucose intolerance and also to a decrease in coenzyme Q10 content of skeletal muscle (29).

A high level of BADL was a positive independent predictor and a high level of comorbidity a negative predictor of increase in Torque peak. Taken together, these findings could be considered an indirect, proxy indicator of frailty, and we know how sarcopenia, which negatively influences muscle strength performance, is a major contributor to frailty (30, 31).

Finally, to attempt at interpreting the results showed in Figure 1, we can identify cut-off baseline values for all three performance indexes under which we can expect to obtain a significant improvement at the end of CR. Conversely, above those values a structured CR program seems to affect only marginally the global functional capacity of elderly patients, probably due to a ceiling effect. Indeed, older cardiac patients with baseline VO_2peak <13 ml/Kg/min, distance walked at 6WT <345 meters, and a Torque peak 90° <55 Newton could be those who obtain major benefit from CR.

Obviously, this hypothesis has to be tested formally in an ad-hoc prospective study, but we believe that these results are interesting to target the patients who may profit the most - in terms of overall improvement in functional capacity - from use of limited health-care resources.

Study limitations: we must underline some limitations, firstly the observational nature of the study, which did not include a control group however the principal aim was identified independent predictors of physical performance in elderly patients. Secondly a further limitation is the use of only 4 weeks of CR, which may not be sufficient to maximize potential gains in aerobic capacity and strength, especially in older adults; nevertheless our CR program reflects the routinely length of rehabilitation provided for the national health care system.

Third, the only 2 measurements (baseline and 4 weeks later) can not exclude the presence of statistical effect named "*regression to the mean*" however the average of improvement is strictly similar to the result obtained by Busch et al. (24) in very old patients attending 3-weeks CR program after Coronary Bypass Surgery. Finally a selection bias could be represent by the exclusion of older patients with significant cognitive decline or disability were excluded, and of those with at least moderate left ventricular dysfunction, which limits our results to only a part of elderly patients routinely hospitalized for cardiac disease

Despite these limitations, we believe that our study demonstrates that a structured CR program, started soon after discharge from acute cardiac medical or post-surgical wards, is safe and produces remarkable improvements in exercise tolerance and muscle strength even in very old cardiac patients. Data also suggest functional baseline cut-off values to be used as criteria for targeting a clinical population of less fit, frail older patients, who are likely to profit the most from CR programs. A result that we deem particularly valuable for optimal utilization of limited health care resources in front of the progressive expansion of the population of older cardiac patients.

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Table legend

Table 1: Clinical characteristics of the study population

Table 2: Differences in clinical characteristics according to be a poor ($\Delta \leq 5\%$) performer in the three indexes of performance

Table 3: Differences in clinical characteristics according to be an excellent ($\Delta > 5\%$) performer in the three indexes of performance

Table 4: Independent predictors of poor ($\leq 5\%$) or excellent (>15%) performance measures at the end of CR (Multivariable logistic regression models)

Figure legend

Figure: Differences in mean basal value at the entry in CR program between poor performers and excellent performers in the three performance indexes

Tables

Table 1

	Mean SD	Range
Age, (yrs)	80.3±4.2	75-93
Body mass index(Kg/m^2)	25.9±3.7	18-40
Heart rate (b/min)	65.8±12.1	41-103
Systolic blood pressure (mmHg)	132.1±21.8	90-195
Diastolic blood pressure (mmHg)	74.5±10.9	50-110
Left Ventricular Ejection Fraction (%)	53.5±8.8	35-74
eGFR (CKDepi formula, cc/min)	**62.3±17.5**	**22-90**
Comorbidity (Charlson-age score)	5.8±1.7	3-10
VO2 peak (ml/kg/min)	**13.9±3.7**	**6.5-26.2**
6WT (mt)	**397.7±93.3**	**140-620**
PT 90° (Newton · mt)	**62.2±23.3**	**10.7-123.1**
	N=	**%**
Male/Female	**113/47**	**70.6/29.4**
~~**Marital status**~~		
~~*Unmarried*~~	~~*9*~~	~~*5.5*~~
~~*Widow/widower*~~	~~*40*~~	~~*25.0*~~
~~*Divorced*~~	~~*3*~~	~~*1.9*~~
~~*married*~~	~~*108*~~	~~*67.5*~~
~~**Education**~~		
~~*Illiterate*~~	~~*2*~~	~~*1.3*~~
~~*Elementary school*~~	~~*87*~~	~~*54.4*~~
~~*Middle school*~~	~~*29*~~	~~*18.1*~~
~~*High school*~~	~~*26*~~	~~*16.3*~~
~~*Graduation degree*~~	~~*16*~~	~~*10.0*~~
Hypertension	123	76.9
Obesity	22	13.8
Diabetes	39	24.4
Hypercolesterolemia	64	40.0
COPD	**17**	**10.6**
Depression	28	17.5
Smoking	40	25.0
	n	**%**
ACE-inhibitors/ARB	144	90.0
Beta-blockers	128	80.0
Antiplatelet agents	143	89.4
Statins	140	87.5

Table 2

Variable	Δ VO2*			Δ 6WT			Δ PTdx		
	≤5% N=65	>5% N=89	p	≤5% N=60	>5% N=100	p	≤5% N=42	>5% N=118	p
Age	80.8±4.4	80.0±4.2	0.250	81.1±4.3	79.8±4.1	0.053	80.1±4.4	80.3±4.2	0.814
Charlson age score	5.6±1.5	5.8±1.8	0.438	5.9±1.6	5.7±1.7	0.481	6.0±1.8	5.7±1.6	0.374
BADL	5.8±0.6	5.9±0.5	0.286	5.8±0.7	5.8±0.4	0.854	5.8±0.4	5.9±0.6	0.537
IADL	7.1±1.5	7.3±1.1	0.524	7.2±1.3	7.1±1.4	0.964	7.1±1.2	7.1±1.2	0.915
MMSE score	27.8±2.2	27.9±2.0	0.764	27.7±2.1	27.9±2.2	0.726	28.0±1.7	27.8±2.3	0.466
GDS score	3.3±3.0	3.3±2.9	0.961	3.3±2.1	3.3±3.0	0.967	3.8±3.2	3.1±2.9	0.174
BMI	25.7±3.9	26.1±3.3	0.524	26.2±3.4	25.7±3.8	0.381	26.7±4.2	25.5±3.9	0.089
Ejection fraction	53.8±9.4	53.5±8.4	0.851	53.8±9.4	53.5±8.4	0.572	53.3±9.0	53.5±8.4	0.553
eGFR (CKDepi-cc/min)	**64.9±16.3**	**60.5±18.2**	**0.120**	**62.7±15.5**	**62.2±18.7**	**0.876**	**63.9±18.4**	**61.9±17.3**	**0.517**
Females	21(32.3)	25(28.1)	0.572	16 (26.7)	31(31.0)	0.560	11(26.2)	36(30.8)	0.577
Diagnosis			0.171			0.440			0.751
ACS (126)	83.1	77.5		80.1	78.0		81.0	77.8	
CABG (23)	7.7	19.1		11.6	16.0		11.9	15.4	
VALV (11)	9.2	3.4		8.3	6.0		7.1	6.8	
Hypertension	76.9	79.8	0.670	76.7	77.0	0.961	73.8	77.8	0.602
Obesity	9.2	16.9	0.173	9.2	14.0	0.906	19.0	11.1	0.193
Diabetes	18.5	29.2	0.126	25.0	24.0	0.887	26.2	23.9	0.770
Sedentary	15.4	13.5	0.739	10.0	18.0	0.170	14.3	14.5	0.969
Dislipidemia	38.5	43.8	0.505	36.7	42.0	0.505	40.5	40.2	0.972
Depression	20.0	14.6	0.378	10.0	22.0	0.053	23.8	15.4	0.219
Smoking	26.3	23.6	0.716	25.0	25.0	1.000	21.4	26.5	0.516
COPD	**10.8**	**10.1**	**0.895**	**62.7**	**18.7**	**0.208**	**14.3**	**9.4**	**0.381**
Antiplatelets	87.7)	91.0)	0.505	90.0)	89.0)	0.942	85.7	90.6.	0.380
ACE/ARB	89.2)	91.0)	0.713	91.7)	89.0)	0.568	85.7	91.5.	0.289
Betablockers	75.4)	83.1)	0.235	76.7)	82.0)	0.414	73.8	82.1	0.253
Statins	81.5)	92.1)	**0.048**	85.0)	89.0)	0.459	81.0	89.7	0.141

Table 3

Variable	Δ VO2*			Δ 6WT			Δ PTdx		
	≤ 15% N=113	>15% N=47	p	≤ 15% N=115	>15% N=45	p	≤ 15% N=82	>15% N=77	p
Age	80.4±4.3	80.0±4.2	0.792	80.4±4.4	79.8±3.8	0.428	80.0±4.3	80.5±4.1	0.396
Charlson age score	5.7±1.6	6.0±1.8	0.316	5.8±1.7	5.7±1.6	0.652	6.0±1.8	5.5±1.5	**0.045**
BADL	5.8±0.5	5.9±0.6	0.304	5.8±0.6	5.8±0.5	0.717	5.7±0.6	5.9±0.4	**0.038**
IADL	7.2±1.3	7.2±1.2	0.951	7.1±1.3	7.2±1.5	0.843	7.0±1.5	7.3±1.1	0.276
MMSE score	27.9±2.0	27.8±2.3	0.882	27.7±2.2	28.3±2.0	0.103	27.9±2.1	27.7±2.2	0.580
GDS score	3.3±2.9	3.1±3.0	0.628	3.1±2.6	3.8±3.4	0.188	3.6±3.2	2.9±2.6	0.175
BMI	25.9±3.8	26.1±2.9	0.724	25.6±3.7	26.5±3.8	0.184	26.3±3.8	25.3±2.3	**0.050**
Ejection fraction	53.8±8.9	53.3±8.7	0.727	54.3±8.4	51.9±9.7	0.129	54.0±8.4	53.1±9.3	0.513
eGFR(CKDepi cc/min)	**63.5±16.7**	**59.7±19.3**	**0.208**	**62.9±16.7**	**61.0±19.6**	**0.550**	**63.5±16.7**	**63.8±18.5**	**0.320**
Females	33(30.8)	13(27.7)	0.691	28(24.3)	19(42.2)	**0.026**	23(28.0)	24(31.2)	0.667
Diagnosis			0.171			0.212			0.141
ACS (126)	83.1	72.3		80.4	75.5		81.7	75.3	
CABG (23)	11.4	23.4		12.6	17.8		11.0	18.2	
VALV (11)	6.5	4.3		7.0	6.7		7.3	6.5	
Hypertension	76.6	83.0	0.377	79.1	71.1	0.279	72.0	81.8	0.141
Obesity	13.1	14.9	0.763	13.0	15.6	0.678	17.1	9.1	0.137
Diabetes	22.4	29.8	0.329	29.6	11.1	**0.015**	30.5	18.2	0.071
Sedentary	15.9	10.6	0.391	11.3	24.4	**0.036**	13.4	15.6	0.697
Dislipidemia	38.3	48.9	0.218	38.3	44.4	0.473	46.3	33.8	0.106
Depression	16.8	17.0	0.976	13.0	28.9	**0.018**	22.0	13.0	0.138
Smoking	29.0	14.9	0.062	25.2	24.4	0.919	22.0	28.6	0.336
COPD	**12.1**	**6.5**	**0.280**	**10.4**	**11.1**	**0.904**	**12.2**	**9.1**	**0.527**
Antiplatelets	90.7	87.2	0.522	90.4	86.7	0.487	78.4	93.5	0.097
ACE/ARB	91.6	87.2	0.401	89.6	91.1	0.769	90.2	89.6	0.894
Betablockers	78.5	83.0	0.524	81.7	75.6	0.379	78.0	81.8	0.554
Statins	86.9	89.4	0.671	88.7	84.4	0.465	82.9	92.2	0.078

Table 4

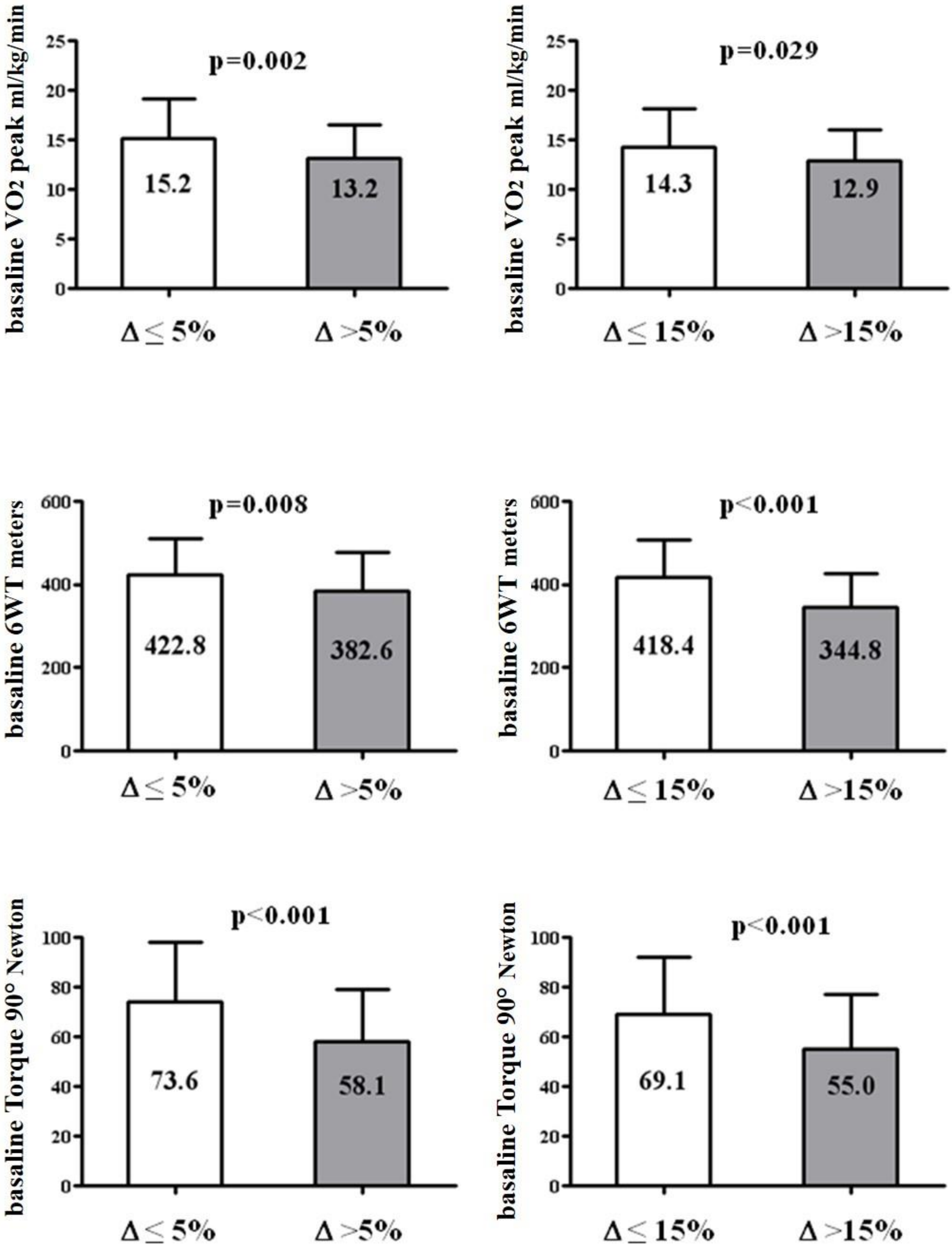
Independent variables	Δ VO_2peak ≤ 5%		Δ VO_2peak >15%	
	Wald χ^2 R	**OR (95%CI)**	**Wald χ^2 R**	**OR (95%CI)**
Age	6.55	1.12 (1.03-1.23) §	1.39	0.95 (0.87-1.04)
Female gender	2.43	0.53 (0.24-1.18)	1.27	1.60 (0.71-3.60)
Baseline VO_2peak	14.45	1.24 (1.11-1.39) ¶	6.59	0.86 (0.77-0.97) ¶
Statins	3.94	2.87 (1.01-8.13) #	…….	………………..

Independent variables	6 WT ≤ 5%		6 WT >15%	
	Wald χ^2R	**OR (95%CI)**	**Wald χ^2R**	**OR (95%CI)**
Age	7.13	1.13 (1.03-1.23) §	3.08	0.92 (0.83-1.01)
Female gender	0.52	0.74 (0.33-1.68)	0.28	0.80 (0.35-1.86)
Baseline 6WT	8.96	1.01 (1.00-1.01) §	13.65	0.99 (0.99-1.00) ¶
Depression	1.18	1.75 (0.64-4.85)	1.35	0.57 (0.22-1.47)
Sedentary Lifestyle	…….	……………….	0.01	0.98 (0.34-2.83)

Independent variables	PT 90° ≤ 5%		PT 90° >15%	
	Wald χ^2R	**OR (95%CI)**	**Wald χ^2R**	**OR (95%CI)**
Age	1.36	1.06 (0.96-1.17)	0.01	1.00 (0.92-1.09)
Female gender	1.94	0.51 (0.19-1.32)	2.75	2.06 (0.88-4.85)
Basal PT 90°	14.31	1.04 (1.02-1.06) ¶	15.58	0.96 (0.94-0.98) ¶
Charlson index	…….	………………..	6.32	0.75 (0.60-0.93) #
BADL	…….	………………..	4.49	2.60 (1.07-6.27) #
BMI	…….	………………..	0.51	0.96 (0.87-1.07)

 # $p<0.05$
§ $p<0.01$
¶ $p<0.001$

Figure



basaline VO2 peak ml/kg/min
p=0.002
15.2
13.2
Δ ≤ 5%
Δ >5%
basaline VO2 peak ml/kg/min
p=0.029
14.3
12.9
Δ ≤ 15%
Δ >15%
basaline 6WT meters
p=0.008
422.8
382.6
Δ ≤ 5%
Δ >5%
basaline 6WT meters
p<0.001
418.4
344.8
Δ ≤ 15%
Δ >15%
basaline Torque 90° Newton
p<0.001
73.6
58.1
Δ ≤ 5%
Δ >5%
basaline Torque 90° Newton
p<0.001
69.1
55.0
Δ ≤ 15%
Δ >15%