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# Improved Exercise Tolerance and Quality of Life With Cardiac Rehabilitation of Older Patients After Myocardial Infarction

## Results of a Randomized, Controlled Trial

Niccolò Marchionni, MD; Francesco Fattirolli, MD; Stefano Fumagalli, MD; Neil Oldridge, PhD; Francesco Del Lungo, MD; Linda Morosi, MD; Costanza Burgisser, MD; Giulio Masotti, MD

**Background**—Whether cardiac rehabilitation (CR) is effective in patients older than 75 years, who have been excluded from most trials, remains unclear. We enrolled patients 46 to 86 years old in a randomized trial and assessed the effects of 2 months of post-myocardial infarction (MI) CR on total work capacity (TWC, in kilograms per meter) and health-related quality of life (HRQL).

**Methods and Results**—Of 773 screened patients, 270 without cardiac failure, dementia, disability, or contraindications to exercise were randomized to outpatient, hospital-based CR (Hosp-CR), home-based CR (Home-CR), or no CR within 3 predefined age groups (middle-aged, 45 to 65 years; old, 66 to 75 years; and very old, >75 years) of 90 patients each. TWC and HRQL were determined with cycle ergometry and Sickness Impact Profile at baseline, after CR, and 6 and 12 months later. Within each age group, TWC improved with Hosp-CR and Home-CR and was unchanged with no CR. The improvement was similar in middle-aged and old persons but smaller, although still significant, in very old patients. TWC reverted toward baseline by 12 months with Hosp-CR but not with Home-CR. HRQL improved in middle-aged and old CR and control patients but only with CR in very old patients. Complications were similar across treatment and age groups. Costs were lower for Home-CR than for Hosp-CR.

**Conclusions**—Post-MI Hosp-CR and Home-CR are similarly effective in the short term and improve TWC and HRQL in each age group. However, with lower costs and more prolonged positive effects, Home-CR may be the treatment of choice in low-risk older patients. (*Circulation*. 2003;107:2201-2206.)

**Key Words:** aging ■ coronary disease ■ exercise ■ myocardial infarction ■ quality of life

Cardiac rehabilitation (CR) after myocardial infarction (MI) improves exercise tolerance, coronary risk factors, psychological well-being, and health-related quality of life (HRQL) in randomized, controlled trials.<sup>1</sup> Meta-analyses suggest that CR also reduces long-term mortality,<sup>2,3</sup> but none of the 4300-plus patients in the 2 earlier meta-analyses<sup>2,3</sup> and none of the 7600-plus patients in the most recent meta-analysis<sup>4</sup> were older than 75 years. Furthermore, in the most recent trial of CR in the elderly, the average age was only 71 years.<sup>5</sup> Such a limited generalizability of results of CR trials to the older population identifies an important research gap.<sup>1</sup>

Only limited age-specific data are available from trials with an average patient age <75 years<sup>5-13</sup> and from observational studies of post-MI CR with small numbers of patients >75 years of age.<sup>14-16</sup> In particular, whether CR improves exercise tolerance similarly in patients younger and older

than 75 years remains uncertain. Indeed, with only 6% of 778 patients >75 years of age in the largest observational study,<sup>16</sup> its conclusion of a similar percent improvement in exercise tolerance after training in patients younger and older than 75 years is questionable. Furthermore, whether CR has positive effects on HRQL<sup>6,17</sup> has received limited attention in older post-MI patients.<sup>5</sup>

Mobility problems and difficulties in using public transportation may limit the participation in outpatient, supervised, hospital-based CR (Hosp-CR) of older individuals for whom home-based CR (Home-CR) might be a valid alternative. In selected low-risk, middle-aged post-MI patients, Home-CR is safe and effective,<sup>18</sup> but its feasibility and efficacy have never been explored in older adults.<sup>19-22</sup>

We designed the Cardiac Rehabilitation in advanced Age (CR-AGE) randomized trial to test the hypothesis that 2

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months of post-MI Hosp-CR or Home-CR would improve exercise tolerance (primary outcome) compared with no CR (control) and that the extent of this improvement would be independent of age. Secondary objectives of the trial included a comparison of the effects of Hosp-CR and Home-CR on HRQL and on healthcare utilization.<sup>23</sup>

## Methods

### Patients

The trial design has been detailed elsewhere.<sup>23</sup> Patients older than 45 years consecutively referred to our CR unit by 4 of the 6 intensive care units in the Florence area for functional evaluation 4 to 6 weeks after MI over a 48-month period were eligible if they had none of the following exclusion criteria: severe cognitive impairment or physical disability, left ventricular ejection fraction <35%, contraindications to vigorous physical exercise, eligibility for myocardial revascularization because of low-effort myocardial ischemia, refusal, or living too far from the CR unit. An ad hoc ethics committee approved the trial, informed consent was systematically obtained, and a letter describing the trial design was delivered to patients' family physicians.

An age- and gender-stratified factorial design was used, with 3 age groups predefined as middle-aged (45 to 65 years), old (66 to 75 years), and very old (>75 years). Age >75 years identified the very old patients because they traditionally have been excluded from CR trials and are characterized by high healthcare utilization.<sup>24</sup> Within each age group, participants were randomized to Hosp-CR, Home-CR, or no CR. The proportion of men and women in the resulting 9 cells was predefined to ensure across age groups the same gender distribution observed in our unit over the year before study onset. Eligible patients were enrolled until 30 were included in each predefined cell.

Based on the average 1364-kg · m increment in total work capacity (TWC) from baseline observed in a previous controlled, nonrandomized trial of post-MI CR in patients younger and older than 65 years,<sup>7</sup> a sample size of 27 patients in each cell (incremented to 30 to allow a 10% dropout rate) was estimated as necessary to detect (power=0.90; alpha=0.05) an effect of CR on TWC. Given published data in patients younger and older than 70 years<sup>14</sup> or 75 years,<sup>25</sup> we assumed that this estimate would apply also to patients older than 75 years.

### Intervention

The American College of Sports Medicine guidelines were used for exercise prescription.<sup>26</sup> The Hosp-CR program consisted of 40 exercise sessions: 24 sessions (3/wk) of endurance training on a cycle ergometer (5-minute warmup, 20-minute training at constant workload, 5-minute cool down, and 5-minute postexercise monitoring) plus 16 (2/wk) 1-hour sessions of stretching and flexibility exercises. In both sessions, ECG was monitored by telemetry, and exercise intensity was set at 70% to 85% of heart rate attained during baseline symptom-limited exercise test. Patients received cardiovascular risk factor management counseling twice per week and were invited to join a monthly support group together with family members.

Patients randomized to Home-CR participated in 4 to 8 supervised instruction sessions in the CR unit, where they were taught necessary precautions and how to perform their training at home. Patients received cardiovascular risk factor management counseling at each in-hospital session and were invited to join a monthly family-oriented support group. After the instruction phase, patients received an exercise prescription similar to that of the Hosp-CR group, a wristwatch digital pulse monitor, a cycle ergometer, and a log book to record the heart rate attained during each exercise session and reasons for not finishing or missing a session. A physical therapist made home visits every other week to adjust if necessary the exercise prescription, to enhance adherence with intervention, and to record the number of completed sessions and distance cycled. At the end of the 2-month training period, the cycle ergometer was made available

for additional patients randomized to Home-CR. Patients randomized to no CR attended a single structured education session on cardiovascular risk factor management with no exercise prescription and were referred back to their family physicians.<sup>23</sup>

### Data Collection

With the exception of HRQL, baseline data<sup>27</sup> were collected before randomization. Testing personnel were blinded to patient assignment.<sup>23</sup>

TWC was assessed at baseline, at the end of the 2-month program, and 6 and 12 months later (or 8 and 14 months after baseline) by a symptom-limited exercise test on a cycle ergometer (Ergocard II, Esaote) with 25-W workload increments at 3-minute intervals. At each assessment, HRQL was measured with an Italian version of the Sickness Impact Profile (SIP), a generic questionnaire with higher scores meaning greater impact of chronic diseases on daily life activities.<sup>28</sup> This was preferred to disease-specific instruments, which are less sensitive to the impact of comorbidities commonly encountered in older patients.

Fatal and nonfatal events were recorded over the 14-month study period and also were assessed by monthly phone interviews in patients who dropped out of the study at any time. The direct costs of both CR interventions and healthcare utilization (both pharmacological and nonpharmacological), disregarding expenses borne by patients or families, were estimated with Italian health system Diagnosis Related Groups (DRG) figures.

### Statistical Analysis

Data were analyzed with SPSS version 10.1 for Windows, with a 2-sided *P* value <0.05 considered statistically significant. The associations between age and categorical or continuous variables (reported as mean±SEM) were tested by  $\chi^2$  test or 1-way ANOVA. Changes in TWC and SIP score were compared across treatment and age groups with general linear models for repeated measures. Age-treatment interactions were tested by calculating regression models for each outcome variable, with dummy variables for age and treatment groups and interaction terms. With this approach, the difference in the  $-2\log$  likelihood between the 2 nested models approximates a  $\chi^2$  statistic (with degrees of freedom equal to the number of all possible interaction terms) testing for an age-treatment interaction. Baseline data significantly associated with age were entered into multivariate, stepwise linear regression models to identify the determinants of change in TWC from baseline to end of treatment (2 months). The sociodemographic and clinical characteristics, as well as baseline TWC and SIP score, were similar in patients who did and did not complete the trial for any reason. Therefore, we performed a sensitivity analysis comparing results obtained with and without replacement of missing data with data obtained with the expectation-maximization imputation method.<sup>29</sup> Because the 2 analyses provided similar results, which were also similar with missing data substituted with data estimated in a worst-case scenario, only the data from patients who completed the study are presented.

## Results

### Patients

Of 773 screened for eligibility, 270 patients (67.8% males; age range, 46 to 86 years) were enrolled, and 503 (65.1%) were excluded (Figure 1) for cardiological reasons (36.2%), comorbidities that contraindicated vigorous physical exercise (15.0%), disability or cognitive impairment (3.9%), and refusal or logistic reasons (10.0%). More very old patients were excluded (middle-aged 60.0% versus old 59.5% versus very old 72.4%, *P*=0.002) for comorbidities (8.0% versus 15.3% versus 19.6%, *P*<0.001) or disability/cognitive impairment (0.4% versus 2.7% versus 7.1%, *P*<0.001), with similar exclusion rates for cardiological reasons (39.2%

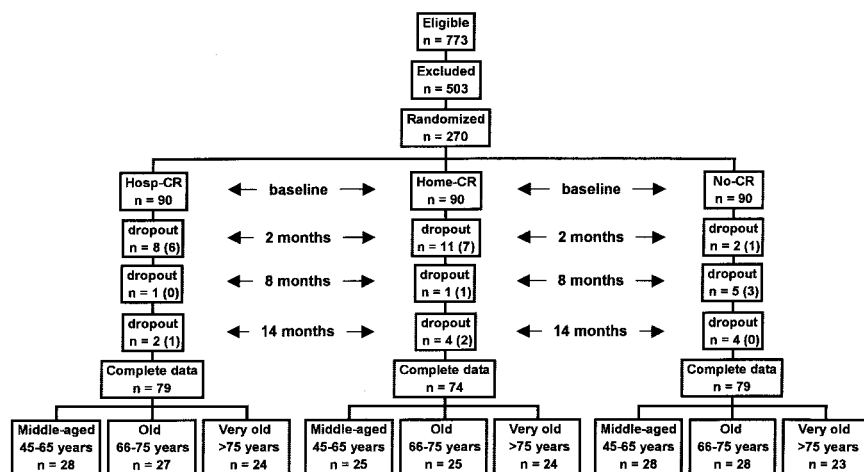


Figure 1. Flowchart of patient randomization and dropout in trial. In parentheses are numbers of dropouts due to refusal.

versus 32.9% versus 37.4%,  $P=0.965$ ) and for refusal or logistic reasons (13.3% versus 8.6% versus 8.3%,  $P=0.061$ ).

In total, 38 patients (14.1%) dropped out (Figure 1): 10 died (1 sudden death, 2 reinfarction, 3 neoplasm, 1 pulmonary embolism, 1 perioperatively after CABG, and 2 undetermined), 7 had nonfatal events (2 reinfarction, 2 CABG, 1 unstable angina, 1 congestive heart failure, and 1 new onset of cognitive problems), and 21 refused to continue the study (14 of 21 within the first 2 months). In this last group, 2 additional events (1 nonfatal reinfarction, 1 unstable angina requiring PTCA) occurred during the follow-up. The dropout rate was greater ( $P=0.043$ ) in the Home-CR group (16/90) than in the Hosp-CR group (11/90) or no-CR group (11/90) and was marginally greater in very old patients (middle-aged 10/90 versus elderly 9/90 versus very old 19/90,  $P=0.071$ ). The number of completed training sessions was similar across treatment and age groups (Hosp-CR: middle-aged  $34\pm 0.5$  versus elderly  $35\pm 0.5$  versus very old  $34\pm 0.4$ ,  $P=0.531$ ; Home-CR: middle-aged  $37\pm 0.3$  versus elderly  $38\pm 0.2$  versus very old  $37\pm 0.5$ ,  $P=0.193$ ).

**Baseline**

There were significant age trends for gender, body weight and body mass index, marital and educational status, smoking, hyperlipidemia, pre-MI physical activity level, sensory deficits, and history of transient ischemic attacks (Table 1). In the entire series and within each age stratum, baseline sociodemographic and clinical characteristics were similar across the 3 arms of the trial (analysis not shown). Baseline TWC was lower in older patients in each study arm but similar within each age group by treatment assignment (Table 2). Baseline SIP scores were similar across age groups, but in middle-aged and very old patients, they were higher (ie, worse) in the Hosp-CR than in the other study arms (Table 2).

**Treatment Effects**

Over the 14-month duration of the trial, TWC improved in the Hosp-CR and Home-CR groups but not in controls (Figure 2), with no significant difference between Hosp-CR and Home-CR. Significant treatment-time interactions confirmed a greater effect of both active interventions compared with no CR in middle-aged and old patients but not in very old

patients (Figure 2), which suggests a lower enhancement in TWC at older age. No significant age-treatment interaction (analysis not shown) was found for changes in TWC, which suggests that the 2 active interventions were equally less effective in older patients. Despite this, at 2 months, TWC had improved significantly in very old patients with both interventions (Figure 2). A multivariate linear regression model that included all baseline variables associated with age confirmed that male gender, assignment to either active treatment versus no CR, and lower age positively predicted changes in TWC from baseline to the end of intervention (Table 3). With Hosp-CR, TWC remained higher than at baseline over the entire study duration only in middle-aged patients, whereas in old and very old patients, it returned toward baseline values at the 6- and 12-month follow-up. Conversely, with Home-CR, TWC remained higher than at baseline over the entire study duration in all age groups (Figure 2). In middle-aged and old patients, HRQL improved significantly over the entire study duration regardless of treatment assignment, whereas in very old patients, HRQL improved significantly with either active treatment but not with no CR (Figure 2).

**Treatment Costs**

Direct costs (in US dollars 2000), calculated as the sum of CR program and healthcare utilization costs over the study duration, amounted to \$21 298 (\$8841+\$12 457) for Hosp-CR, \$13 246 (\$1650+\$11 596) for Home-CR, and \$12 433 (healthcare utilization costs only) for no CR. Fewer medical visits ( $6.5\pm 0.5$  versus  $7.1\pm 0.6$  versus  $9.2\pm 0.9$ ,  $P=0.018$ ) and rehospitalizations ( $0.33\pm 0.07$  versus  $0.46\pm 0.10$  versus  $0.49\pm 0.10$ ,  $P=0.492$ ) in Home-CR compared with Hosp-CR and no-CR patients contributed, at least in part, to produce the differences.

**Discussion**

The results of this trial confirmed our first study hypothesis that compared with no CR, post-MI CR enhances exercise tolerance in patients of all ages, including those older than 75 years and as old as 86 years, who have been excluded from most previous trials.<sup>2-4</sup> Our second study hypothesis was not confirmed. Previous nonrandomized controlled<sup>7,8</sup> and obser-

**TABLE 1. Baseline Characteristics of 270 Enrolled Patients**

Variable	Age, y			P
	45–65 (n=90)	66–75 (n=90)	>75 (n=90)	
<b>Demographic</b>				
Age, y	57±0.6	70±0.3	80±0.3	...
Males, %	85.6	66.7	60.0	0.001
Body weight, kg	77±1.2	70±1.2	65±1.0	0.001
Body mass index, kg/m <sup>2</sup>	27.0±0.4	25.9±0.4	24.8±0.4	0.001
<b>Social, %</b>				
Married	85.4	74.4	59.1	0.001
Education >8 years	59.8	42.7	29.5	0.001
<b>CHD risk factors, %</b>				
Smoking	55.1	20.0	9.1	0.001
Diabetes	13.5	12.2	23.2	0.087
Hyperlipidemia	88.1	76.1	64.4	0.001
Hypertension	40.4	42.2	52.2	0.121
Low pre-MI physical exercise, %	37.5	65.2	72.4	0.001
<b>MI severity</b>				
Anterior MI, %	33.3	35.6	31.1	0.440
CPK <sub>peak</sub> , IU/L	1626±160	1585±152	1243±95	0.104
LVEF	0.52±0.01	0.51±0.01	0.51±0.01	0.809
<b>Comorbidity, %</b>				
Osteoarthritis	4.5	10.0	12.5	0.066
COPD	5.7	12.2	14.8	0.068
Claudication	4.5	12.2	10.2	0.193
Sensory defect	4.5	10.0	22.7	0.001
Transient ischemic attack	1.1	2.2	13.6	0.001

CHD indicates coronary heart disease; CPK<sub>peak</sub>, peak creatine phosphokinase activity; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; and sensory defect, hearing and/or visual loss.

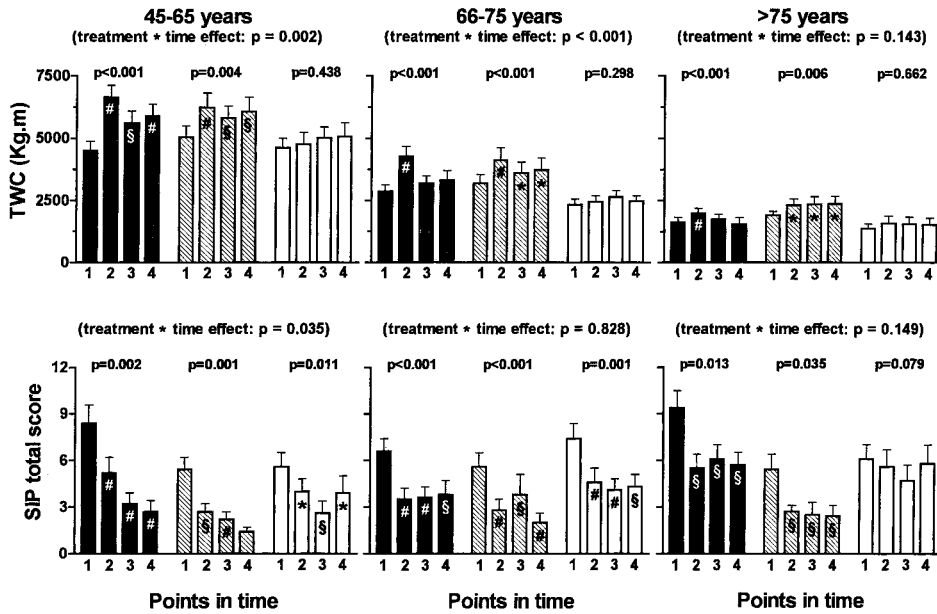
ational<sup>14–16</sup> studies suggest age-independent improvements in exercise tolerance with CR in patients younger and older than 65 years. In fact, in the present trial, TWC improved consistently more with treatment in middle-aged and old patients than in very old patients, and this observation would

not have been detected without having enrolled patients older than 75 years. Accordingly, age was not retained in a multivariate model to predict changes in TWC, in which we excluded very old patients (data not shown), which confirms the limited generalizability of previous studies that reported

**TABLE 2. Baseline TWC and SIP Score, by Age and Treatment Group**

Variable	Age, y			P*
	45–65 (n=90)	66–75 (n=90)	>75 (n=90)	
<b>TWC, kg · m</b>				
Hosp-CR (n=90)	4648±362	2880±244	1652±174	0.001
Home-CR (n=90)	4732±398	2984±302	1843±137	0.001
No CR (n=90)	4397±348	2380±208	1416±146	0.001
P†	0.801	0.206	0.147	...
<b>SIP total score</b>				
Hosp-CR (n=90)	8.4±1.1	6.6±0.7	8.8±1.0	0.223
Home-CR (n=90)	5.6±0.7	5.8±0.7	5.3±0.8	0.904
No CR (n=90)	5.5±0.8	7.5±1.0	6.2±0.8	0.253
P†	0.029	0.318	0.017	...

\*Between age groups; †between treatment groups.



**Figure 2.** Changes in exercise tolerance (TWC; top) and quality of life (SIP; bottom) by age and treatment assignment from baseline (1) to 2 months (end of intervention; 2) to 8 and 14 months after enrollment (3 and 4). Black bars indicate Hosp-CR; hatched bars, Home-CR; open bars, no CR. # $\$^*P < 0.001$ , 0.01, and 0.05 vs baseline, respectively.

age-independent improvements in exercise tolerance with CR.<sup>7,8,14-16</sup> Furthermore, the results suggest that a 2-month CR program may be too short to obtain the optimal physiological benefits in patients older than 75 years.

As previously observed,<sup>17</sup> HRQL improved in both of the younger cohorts in the present study with and without CR, which indicates a spontaneous improvement in state of health perception after recovery from MI. Conversely, in very old patients, HRQL was enhanced only with active treatments, which reinforces the view that CR is particularly useful in older patients who have been excluded from most previous trials.<sup>2-4</sup>

The question of the long-term effect of CR on exercise tolerance is important. As in previous trials,<sup>17</sup> in the present study, most of the initial improvement in TWC observed with Hosp-CR was lost over the 12-month follow-up. Conversely, in each age group, the improvement was better preserved in the long term with Home-CR. Although we do not have specific information on changes in physical activity after CR, this finding suggests that Home-CR, with implicit self-management of the exercise program, induces a permanent

change in lifestyle more effectively than Hosp-CR. Adherence was similar in both interventions, with no treatment- or age-associated difference in the cumulative incidence of new events. All these observations extend the efficacy and safety of Home-CR for carefully selected, younger post-MI patients to patients up to at least 86 years of age.<sup>18,20</sup> Furthermore, it is important to stress that Home-CR in the present trial was associated with remarkable cost savings, which originated from both lower program costs and reduced healthcare utilization by patients assigned to CR in general and to Home-CR in particular.

Study limitations are acknowledged. The high exclusion rate, which resulted from the selection of patients who could exercise safely at home,<sup>23</sup> may limit the generalizability of this trial. On the other hand, we believe that the restrictive eligibility criteria, together with carefully monitored exercise prescription intensity, resulted in few events, none related to exercise, even in patients who exercised at home. Importantly, most of the dropouts occurred during the first 2 months of the trial and were not due to training-related events but to refusals to continue in the trial.

Although the cumulative 14.1% dropout rate over the 14-month study period may be regarded as a limitation, dropout was only 7.8% during the first 2 months, well below the 10% dropout rate accounted for in sample-size calculations targeted at first study hypothesis. Furthermore, because baseline data were similar in those who did and did not complete the study, we exclude the potential bias of selective dropout of sicker patients.

A further potential limitation is that in middle-aged and very old patients, baseline SIP scores, based on self-assessment of changes in health status attributable to chronic diseases,<sup>28</sup> were higher in Hosp-CR than in either other randomization group. In the present trial, the SIP was administered soon after baseline evaluation and randomization, and knowledge of assignment to Hosp-CR, with the implication that care in the hospital setting was still needed,

**TABLE 3. Multivariate Determinants of Change ( $\Delta$ ) in TWC From Baseline to 2 Months (End of Intervention)**

Variables	$\Delta$ TWC, kg · m ( $r=0.490$ ; $P=0.001$ )		
	$\beta$	SE $\beta$	$P$
Constant	3079.2	560.3	...
Age (per 10 years)	-330.0	81.0	0.001
Gender (F=2 vs M=1)	-463.4	173.8	0.008
Hosp-CR vs No CR	1089.4	182.5	0.001
Home-CR vs No CR	606.9	188.7	0.001

Variables excluded ( $P > 0.10$ ) from the model: body weight; being married; education  $> 8$  years; smoking; hyperlipidemia; pre-MI physical activity; history of osteoarthritis, chronic obstructive pulmonary disease, stroke, or transient ischemic attack; hearing/visual loss; baseline TWC; and body mass index.

may have negatively influenced patients' perception of their health. However, this potential bias should not have influenced changes in SIP from baseline.

Finally, inadequate sample size may have resulted in the similar short-term improvement in TWC with Hosp-CR and Home-CR. However, this limits neither the conclusion of the superiority of CR over no CR nor the evidence of feasibility of CR in general in patients older than 75 years.

Despite these limitations, the CR-AGE trial provides original information on the efficacy of post-MI CR in older patients. First, we demonstrated that the physiological response to CR is attenuated in patients older than 75 years. Additional research will demonstrate whether very old patients need a longer duration of CR for optimal physiological benefit. Second, the need for designing CR interventions with less rigid admission criteria and a lower intensity exercise prescription<sup>1</sup> is reinforced by the age-related increase in the exclusion rate from the present trial. Finally, the present findings suggest that post-MI Home-CR is cost-effective and may be preferable in very old, low-risk patients. Assignment of lower-risk individuals to Home-CR programs would imply that larger numbers of medium- and high-risk, frail older patients would have access to the limited available resources presently concentrated on Hosp-CR.

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