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CLINICAL RESEARCH
Coronary artery disease

Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: a long-term follow-up study

Sara Doimo[1], Enrico Fabris[1]*, Massimo Piepoli[2], Giulia Barbati[3], Francesco Antonini-Canterin[4], Guglielmo Bernardi[5], Patrizia Maras[1], and Gianfranco Sinagra[1]

[1]Cardiovascular Department, Azienda Sanitaria Universitaria Integrata, University of Trieste, Via Pietro Valdoni n. 7, 34149 Trieste, Italy; [2]Heart Failure Unit, Cardiac Department, Guglielmo da Saliceto Hospital, Piacenza, Italy; [3]Biostatistics Unit, Department of Medical Sciences, University of Trieste, Italy; [4]Cardiovascular Rehabilitation, Ospedale Riabilitativo di Alta Specializzazione, Motta di Livenza, Italy; and [5]Division of Cardiology, "Santa Maria degli Angeli" Hospital, Pordenone, ASS5, Italy

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Aims To evaluate the long-term clinical impact of the application of cardiac rehabilitation (CR) early after discharge in a real-world population.

Methods and results We analysed the 5-year incidence of cardiovascular mortality and hospitalization for cardiovascular causes in two populations, attenders vs. non-attenders to an ambulatory CR program which were consecutively discharged from two tertiary hospitals, after ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, coronary artery bypass graft, or planned percutaneous coronary intervention. A primary analysis using multivariable regression model and a secondary analysis using the propensity score approach were performed. Between 1 January 2009 and 31 December 2010, 839 patients attended a CR program planned at discharged, while 441 patients were discharged from Cardiovascular Department without any program of CR. During follow-up, the incidence of cardiovascular mortality was 6% in both groups ($P = 0.62$). The composite outcome of hospitalizations for cardiovascular causes and cardiovascular mortality were lower in CR group compared to no-CR group (18% vs. 30%, $P < 0.001$) and was driven by lower hospitalizations for cardiovascular causes (15 vs. 27%, $P < 0.001$). At multivariable Cox proportional hazard analysis, CR program was independent predictor of lower occurrence of the composite outcome (hazard ratio 0.55, 95% confidence interval 0.43–0.72; $P < 0.001$), while in the propensity-matched analysis CR group experienced also a lower total mortality (10% vs. 19%, $P = 0.002$) and cardiovascular mortality (9% vs. 35%, $P = 0.008$) compared to no-CR group.

Conclusion This study showed, in a real-world population, the positive effects of ambulatory CR program in improving clinical outcomes and highlights the importance of a spread use of CR in order to reduce cardiovascular hospitalizations and cardiovascular mortality during a long-term follow-up.

Keywords Coronary artery disease • Cardiac rehabilitation • Cardiovascular mortality • Cardiovascular hospitalization • Propensity score

Introduction

Cardiac rehabilitation (CR) program is a multidisciplinary intervention including physical exercise, nutritional advice, lipid and blood pressure control, smoking cessation program, psychological counselling, and target-driven pharmacological therapies.[1–4]

Cardiac rehabilitation after ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), coronary

* Corresponding author. Tel: + 39 040 399 4477, Fax: + 39 040 399 4153, Email: enrico.fabris@hotmail.it

artery bypass graft (CABG), and planned percutaneous coronary intervention (PCI), is a Class IA recommendation from the American Heart Association/American College of Cardiology[5] and the European Society of Cardiology[6,7] guidelines.

Although the efficacy of CR to reduce clinical outcomes has been proven,[8–12] this intervention remains significantly underused. Only about a third of coronary patients in Europe receives any form of CR and only a 25% in the USA.[13–15] Based on data from the EUROASPIRE study of cardiovascular disease management, 44.8% of CR-eligible patients had evidence of referral and 36.5% evidence of participation in rehabilitation.[16,17] In the real-world, the absence of CR program may result in worse clinical outcomes at long-term follow-up.

Therefore, we evaluated the long-term clinical impact of the application of an early CR program planned at discharged compared to a population of the same geographic area who did not receive any CR because CR service was not available.

Methods

Study population

In this study, we analysed clinical and instrumental characteristics and outcomes of two populations, attenders vs. non-attenders to a CR program which were consecutively discharged from two tertiary hospitals, after STEMI, NSTEMI, CABG with or without valve surgery or planned PCI, between 1/1/2009 and 31/12/2010.

Per-protocol, in one hospital all patients discharged from Cardiovascular Department were referred to ambulatory Cardiac Rehabilitation Division with a scheduled visit reported on discharge letter. These patients were unselected, only who were not residents in the region or with severe non-cardiac comorbidities such as end-stage tumours, dementia, or immobilized patients, were excluded. In our population, only 13% of eligible patients did not attend CR.

According to guidelines, patients were enrolled in CR early after discharge: STEMI and CABG patients were convened to the first evaluation within 2 weeks, while NSTEMI and PCI in 4 weeks. At the first CR visit, the clinical profile of the patients, the risk factors, and comorbidities were evaluated and the CR program planned.

In the other tertiary hospital, all patients discharged after STEMI, NSTEMI, CABG, or planned PCI did not receive any CR because CR service was not available. This group is composed by consecutive and unselected patients.

The Ambulatory Rehabilitation Programme

The CR program was performed in a dedicated Cardiac Rehabilitation Division.

The NSTEMI or PCI patients received clinical-instrumental evaluations until achievement of therapeutic and clinical targets, with scheduled visits, cycle-ergometer tests, and echocardiogram. ST-elevation myocardial infarction and CABG patients, in addition, were sent to a physical activity, consisting in a first part of 10 sessions of 45 min of cyclette training two time a week for 5 weeks, and a second part of 18 sessions of 45 min of gym training three time a week for 6 weeks. The average duration of the CR program for the whole population was 5 months.

There were three different levels of physical activity: low, medium, and high. A maximal effort test was used to assess exercise capacity of patients, for insert them in appropriate level of work. The physical session was supervised by a trained nurse and physiotherapist, with continuous cardiac monitoring assessment. Moreover, the CR program was tailored for 'frail' patients, such as very old patients (>80 years) or affected by several comorbidities and functional limitations, with specific physical exercises, clinical, and instrumental evaluations. Each patient had a personal portfolio in which were reported the intensity of exercise and the clinical parameters registered during the physical activity. Patients and physiotherapists could evaluate mutually all progresses or areas of improvement. In this way, the patient played an active role on its health care and the adherence to physical program was promoted.

All groups received counselling about lifestyle during every visit and a nutritional meeting with the nutritionist was scheduled one time a month. Active smokers were assisted by the psychologist in a tailored program to quit smoking. The psychologist was dedicated also to support patients that had difficulty to accept their disease.

After CR, all patients were referred to cardiology ambulatory service, where were periodically visited. This network has permitted a long follow-up of the patients.

Outcomes

The primary outcome of this study was the 5-year composite endpoint incidence of hospitalization for cardiovascular causes and cardiovascular mortality.

Vital status and hospitalization where collected through a regional medical record system and

E-Chart including data collected during routine clinical practice.

Clinical, echocardiographic, and biohumoral data were extracted from the Cardiac Rehabilitation Division Registry,[18,19] for the CR attenders group and from the electronic medical record of Sanitary System for non-attenders to CR.

The study was approved by the institutional review committee and was performed in accordance with the 2000 revised Declaration of Helsinki.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or as median with interquartile range for continuous variables depending on the distribution shape. For continuous variables, differences between two groups were compared using Student's *t*-test or Mann–Whitney *U* test. Categorical variables were expressed as counts and percentages and compared by χ^2 test or Fisher's exact test, when appropriate.

In order to evaluate the prognostic value of attenders CR program vs. non-attenders, we performed a primary analysis using multivariable regression model and a secondary analysis using the propensity score approach.

In the primary analysis, we used univariable and multivariable Cox proportional hazards regression analysis to calculate unadjusted and adjusted hazard ratios and 95% confidence intervals (CIs).

In the secondary analysis, we used a propensity score matching method to reduce the confounding effect due to differences in demographics between the CR participation group and the non-participation group.[20] We estimated a propensity score in order to create 1:1 matched data set (non-rehabilitation vs. rehabilitation) and the covariates considered for balance were age, sex, hypertension, left ventricular ejection fraction (LVEF), diabetes, smoking, dyslipidaemia, chronic kidney disease, previous PCI, previous acute coronary syndrome (ACS), beta-blockers, ACE-inhibitors/ARBs, and Statins/Ezetimibe.

Survival curves in the matched data set were estimated by the Kaplan–Meier method and compared by log-rank tests. The statistical analysis was performed using the IBM-SPSS version 21 (Armonk, NY: IBM Corp) and the R software version 3.3.2 libraries 'rgenoud' and 'Matching'

[R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria].

Results

Baseline characteristics of attenders and non-attenders

Baseline characteristics of the two groups are presented in *Table 1*. From 1 January 2009 to 31 December 2010, 839 patients attended a CR program, while 441 patients were discharged from Cardiovascular Department without any program of CR.

Compared with those who did not attend the CR program, attenders were less frequently male (68% vs. 75% $P = 0.010$), were older (68 ± 11 vs. 66 ± 12 years, $P < 0.001$) with more prevalence of risk factors and comorbidities such as hypertension (76% vs. 68%, $P = 0.001$), smoking (26% vs. 18%, $P = 0.001$), dyslipidaemia (73% vs. 44%, p= <0,001) and chronic renal failure (14% vs. 9%, $P = 0.012$); however, attenders presented less frequently history of previous ACS (18% vs. 27%, $P < 0.001$) and previous PCI (12% vs. 20%, $P < 0.001$). Both groups had a mean LVEF above 50% and patients attending CR had a higher LVEF compared to no attenders (56 ± 11 vs. 52 ± 9 $P < 0.001$). In both groups, there were not differences on the enrolment diagnosis (STEMI, NSTEMI, PCI, and CABG). We reported the features of all subgroups in Supplementary material online, *Table S1*. Only 3.8% of attenders have not completed the program.

Table 1 Baseline characteristics of non-attenders and attenders

	Non-attenders (441 pts)	Attenders (839 pts)	P-value
Age (mean ± SD; years)	66 ± 12	68 ± 11	0.001
Male, % (*n*)	75 (330)	68 (570)	0.010
Elderly (age > 75 years), % (*n*)	20 (90)	27 (225)	0.009
STEMI, % (*n*)	29 (127)	30 (251)	0.709
NSTEMI, % (*n*)	23 (103)	19 (162)	0.089
PCI, % (*n*)	23 (101)	22 (183)	0.655
CABG, % (*n*)	25 (110)	29 (243)	0.126
Hypertension, % (*n*)	68 (299)	76 (639)	0.001
Diabetes, % (*n*)	30 (130)	29 (240)	0.753
Smoking, % (*n*)	18 (77)	26 (218)	0.001
Dyslipidaemia, % (*n*)	44 (193)	73 (613)	<0.001
Chronic kidney disease, % (*n*)	9 (41)	14 (119)	0.012
Ejection fraction (mean ± SD, %)	52 6 9	56 6 11	<0.001
Previous ACS, % (*n*)	27 (121)	18 (150)	<0.001
Previous PCI, % (*n*)	20 (90)	12 (102)	<0.001
Previous CABG, % (*n*)	5 (23)	5 (39)	0.653
Beta-blockers, % (*n*)	96 (422)	72 (600)	<0.001
ACE-inhibitors/ARBs, % (*n*)	97 (429)	68 (570)	<0.001
Statins/ezetimibe, % (*n*)	97 (430)	87 (725)	<0.001
ASA, % (*n*)	97 (428)	96 (799)	0.265
DAPT, % (*n*)	67 (294)	65 (540)	0.511

ACE-inhibitors, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs angiotensin receptor blockers; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; Pts, patients; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

Outcomes

During follow-up, median 82 months, interquartile range [60–89], CR group compared to no-CR group experienced a lower incidence of the composite endpoint of hospitalizations for cardiovascular causes and cardiovascular mortality (18% vs. 30%, $P < 0.01$), however this difference was driven by lower hospitalizations for cardiovascular causes (15% vs. 27%, $P < 0.01$) (*Table 2*). The overall incidence of all-cause mortality (17% vs. 18% in CR vs. no-CR groups, respectively, $P = 0.861$) and cardiovascular mortality (6% vs. 6%, $P = 0.623$) were similar in both groups. The multivariable Cox proportional hazard analysis showed that participation in CR program [hazard ratio (HR) 0.578, 95% CI 0.432–0.773; $P < 0.001$], CABG (HR 0.639, 95% CI 0.466 to 0.876; $P = 0.005$), LVEF (HR 0.986, 95% CI 0.973–0.0.999; $P = 0.035$) and statin/ezetimibe therapy (HR 0.518, 95% CI 0.345–0.776; $P = 0.001$) were independent pr. 1.107 to 1.926, $P = 0.007$) and chronic kidney disease (HR 2.441; 95% CI 1.775 to 3.358, $P < 0.001$) were independently associated with worse outcome (*Table 3*). Estimated survival curves from the Cox model for different types of 'typical' patients are shown in *Figure 1*.

Applying the propensity-matched analysis (*Table 4*), CR group, compared to non-CR group, experienced a lower composite endpoint (hospitalizations for cardiovascular causes and cardiovascular mortality) (13% vs. 29%, $P < 0.001$) or hospitalizations for cardiovascular causes (11% vs. 25% $P < 0.001$). Moreover, both total mortality (10% vs. 19%, $P = 0.002$) and cardiovascular mortality (7% vs. 2%, $P = 0.008$) were lower in CR group compared to no-CR group (*Table 5, Figure 2A,B*). Because it was not possible to obtain a match for variables 'STEMI' and 'NSTEMI', we estimated the Kaplan–Meier curves on matched data stratified for these two parameters in order to evaluate the effect of CR. The Kaplan–Meier curves related to the composite endpoint, cardiovascular mortality and hospitalization, stratified for STEMI are presented in Supplementary material online, *Figure S1*, stratified for the NSTEMI are presented in Supplementary

Table 2 Cardiovascular outcome

	Non-attenders (441 pts)	Attenders (839 pts)	P-value
Total mortality % (*n*)	18 (78)	17 (142)	0.861
Cardiovascular mortality % (*n*)	6 (28)	6 (48)	0.623
Hospitalizations % (*n*)	27 (119)	15 (122)	<0.001
Hospitalization and cardiovascular mortality % (*n*)	30 (133)	18 (155)	<0.001

Pts, patients.

Table 3 Univariable and multivariable analysis (primary analysis Cox)

Variables	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Cardiac rehabilitation	0.601 (0.476–0.758)	<0.001	0.578 (0.432–0.773)	<0.001
NSTEMI	1.361 (1.043–1.774)	0.023		
Male	1.168 (0.898–1.517)	0.246		
STEMI	0.908 (0.701–1.176)	0.463		
PCI	1.343 (1.036–1.742)	0.026		
CABG	0.621 (0.465–0.828)	0.001	0.639 (0.466–0.876)	**0.005**
Ejection fraction	0.979 (0.967–0.991)	0.001	0.986 (0.973–0.999)	**0.035**
Diabetes	1.548 (1.219–1.966)	<0.001	1.460 (1.107–1.926)	**0.007**
Hypertension	1.161 (0.887–1.520)	0.276		
Smoking	1.121 (0.860–1.463)	0.398		
Dyslipidaemia	0.897 (0.708–1.138)	0.372		
Beta-blockers	1. 244 (0.910–1.701)	0.171		
ACE-inhibitors/ARBs	1.367 (1.005–1.859)	0.046		
Statins/ezetimibe	0.607 (0.426–0.865)	0.006	0.518 (0.345–0.776)	**0.001**
ASA	0.932 (0.510–1.703)	0.819		
DAPT	1.245 (0.968–1.601)	0.088		
Chronic kidney disease	2.409 (1.823–3.182)	<0.001	2.441 (1.775–3.358)	<0.001
Previous ACS	1.443 (1.111–1.873)	0.006		
Previous PCI	1.718 (1.299–2.272)	<0.001		
Previous CABG	1.884 (1.240–2.861)	0.003		

ACE-inhibitors, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; CI, confidence interval; DAPT, dual antiplatelet therapy; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

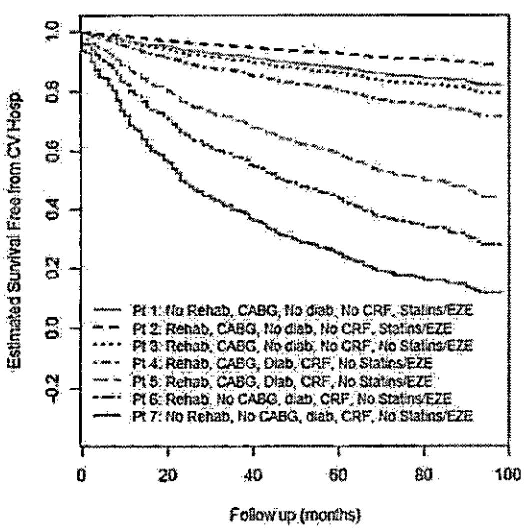

Figure 1 Estimated survival curves from the Cox model. The curves are estimated for patients having the median ejection fraction (56%) of the population. CABG, coronary artery bypass graft; CRF, chronic renal failure; Diab, diabetes; EZE, ezetimibe; Rehab, cardiac rehabilitation.

material online, *Figure S2*; both showed that non-attendance to CR had a significant effect on the prognosis. The relation between values of LVEF and outcome is represented in the Supplementary material online, *Figure S3*.

Similarly, the Kaplan–Meier curves related to the composite endpoint, cardiovascular mortality, and hospitalization, stratified for the previous NSTEMI = 0 or NSTEMI = 1 (Supplementary material online, *Figure S3*) and the Kaplan–Meier curves about hospitalization stratified for the previous NSTEMI = 0 or NSTEMI = 1 (Supplementary material online, *Figure S4*) confirmed that non-CR group had the worse prognosis despite the difference in previous ischaemic cardiovascular events. Finally, the Kaplan–Meier curves stratified for LVEF < or ≥ 50% are presented in Supplementary material online, *Figure S5*, both showing the significant better outcomes of CR group compared to non-CR group.

Discussion

This study, performed on a large cohort of patients, showed that CR participation was independently associated with a reduction of a composite endpoint of hospitalizations for cardiovascular causes and cardiovascular mortality during the first 5 years following an ACS or coronary revascularization.

This study confirmed the efficacy of an ambulatory CR in an unselected real-world population and showed as the evaluation of a CR

Table 4 Baseline characteristics in the propensity-matched analysis

	Non-attenders	Attenders	P-value
Age (mean ± SD)	66 ± 12	66 ± 11	0.488
Male, % (*n*)	74 (272)	75 (275)	0.433
STEMI, % (*n*)	31 (116)	39 (145)	0.031
NSTEMI, % (*n*)	21 (78)	12 (45)	0.002
PCI, % (*n*)	18 (67)	17 (62)	0.698
CABG, % (*n*)	29 (108)	32 (117)	0.522
Hypertension, % (*n*)	67 (248)	71 (261)	0.340
Diabetes, % (*n*)	29 (108)	26 (96)	0.365
Smoking, % (*n*)	17 (63)	13 (49)	0.182
Dyslipidaemia, % (*n*)	42 (153)	39 (145)	0.600
Ejection fraction (mean ± SD)	52 ± 9	52 ± 12	0.302
Chronic kidney disease, % (*n*)	11 (40)	10 (38)	0.905
Previous ACS, % (*n*)	27 (99)	24 (88)	0.397
Previous PCI, % (*n*)	18 (68)	14 (51)	0.109
Previous CABG, % (*n*)	4 (16)	3 (11)	0.433
Beta-blockers, % (*n*)	96 (353)	97 (359)	0.318
ACEi/ARBs, % (*n*)	97 (357)	96 (353)	0.564
Statin/ezetimibe, % (*n*)	98 (360)	97 (359)	0.822

Seventy-two patients had no LVEF values and were excluded from the analysis.
ACEi, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass graft; CRF, chronic renal failure; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; Pts, patients; SD, standard deviation; STEMI, ST-elevation myocardial infarction.

Table 5 Events (propensity-matched analysis)

	Non-attenders	Attenders	P-value
Total mortality, % (*n*)	19 (69)	10 (38)	**0.002**
Cardiovascular mortality, % (*n*)	7 (25)	2 (9)	**0.008**
Hospitalization, % (*n*)	25 (94)	11 (42)	<0.001
Hospitalization and cardiovascular mortality, % (*n*)	29 (106)	13 (48)	<0.001

Seventy-two patients had no left ventricular ejection fraction (LVEF) values and were excluded from the analysis.

program in a geographic area is an essential safeguard to ensure that CR service is delivered effectively. Indeed, the rigorous analysis of the results, highlighted the importance of the utilization of CR, encouraging all Cardiovascular Department to adopt CR as an integral part of standard of care in modern cardiology.

Multiple studies have focused on outcome effects of CR, however, trials were conducted on small population of patients and most of them assessed only combined endpoints or surrogate endpoints and actually, these studies are older than 20 years. For these reasons, results about the impact of CR on coronary patients are derived mainly from meta-analyses. The most recent Cochrane systematic review and meta-analysis on 63 studies with 14 486 participants to CR showed a reduction in pooled cardiovascular mortality and hospital admission with exercise-based CR compared with no-exercise control groups.[12]

In our primary analysis, we showed a significant reduction in hospitalizations and in the combined endpoint of hospitalizations and cardiovascular mortality, but we did not observe a statistically significant reduction in cardiovascular mortality alone, and there was not difference in total mortality, as the Cochrane meta-analysis reported.

In our first analysis, the smaller population, together with the potential presence of unmeasured confounders may account for the absence of a clear mortality benefit between the two groups. However is interesting to note that when we used a propensity score matching method to reduce the confounding effect due to differences in demographics between the CR participation group and the non-participation group,[20] the value of CR was highlighted also in terms of reduction of cardiovascular and total mortality confirming the potential survival benefit of patients attending a CR program[12,21] also in the modern era of treatment of coronary artery disease.[22]

In our study, we showed a significant reduction in hospitalizations and in the combined endpoint of hospitalizations and cardiovascular mortality, but we did not observe a statistically significant reduction in cardiovascular mortality alone, and there was not difference in total mortality, as the Cochrane meta-analysis reported. However, in the previous Cochrane meta-analyses published in 2011, it was observed a significant reduction also in all-causes mortality with CR but actually, this endpoint has not been confirmed. In our population, the absence of difference between the groups in cardiovascular mortality could be related to the era in which these patients have been enrolled. Indeed, we performed the analysis on a recent cohort who received a modern coronary revascularization treatment and a current optimal medical therapy, therefore the strength of CR intervention could be more evident on reduction in hospital admissions. Despite this sentence is in contrast with results of CROS study,[22] the smaller population of our study may explain the different results, nevertheless, the reduction of hospitalizations in a real-world experience is certainly relevant and has an import clinical impact for patients' care.

Moreover, our analysis, were performed on a long-term follow-up, and permitted to demonstrate the long-term benefits of CR. Indeed, the Kaplan–Meier curves diverged mainly at the end of follow-up period, suggesting that the CR is effective for a long time after the treatment. The Cochrane meta-analysis, while confirming the efficacy of CR, underlined that the median follow-up of the published studies was 12 months with only 18 studies reporting a follow-up of 36 months or more.[12] Therefore, the long-term association between CR attendance and clinical outcomes has been studied rarely.[23]

Importantly the results of our study were obtained, according to the international guidelines, with a strategy of early enrolment in which eligible patients were referred to CR with a scheduled visit reported on the discharge letter and within a brief time from hospitalization, in order to avoid any selection of eligible patients and to have a high level of attendance. Indeed, the time of referral plays a key role on the CR attendance. Retrospective studies suggested that

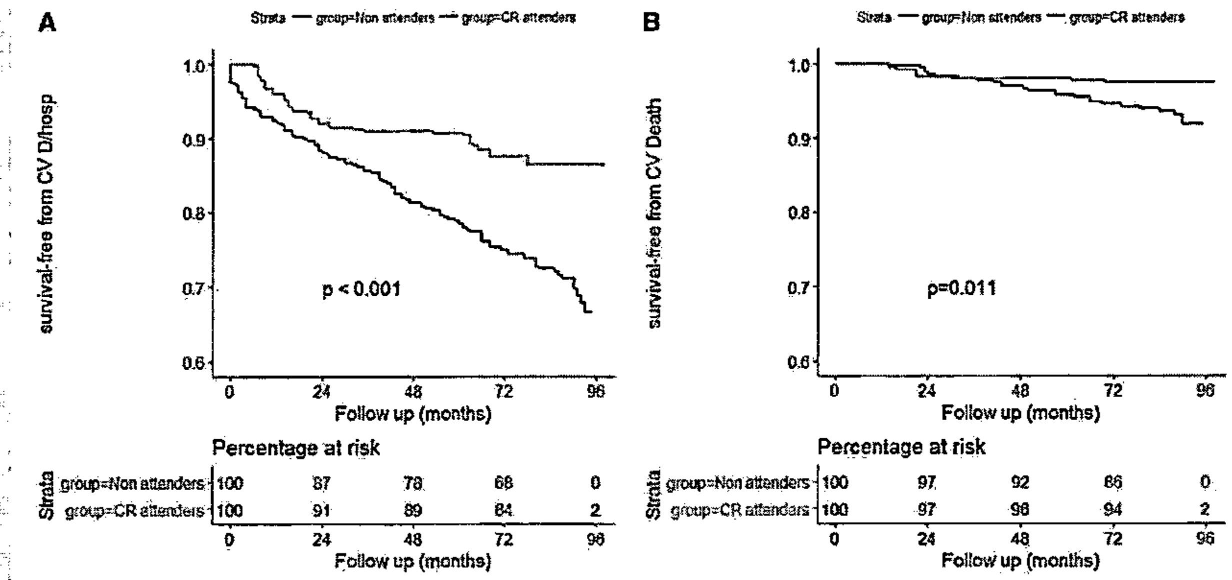

Figure 2 (A) The Kaplan–Meier survival curves for the composite endpoint, cardiovascular hospitalization, and cardiovascular mortality for attenders CR and non-attenders after propensity score analysis. (B) The Kaplan–Meier survival curves for cardiovascular mortality only for attenders CR and non-attenders after propensity score analysis. CR, cardiac rehabilitation.

for every day of delay between hospital discharge and CR, there is an associated 1% decrease in participation[24] and Pack et al.[25] found a significant 18% absolute and 56% relative improvement in attendance in the group of patients with early appointment to CR. A recent study published by Mayo Clinic showed that through the use of system-based approaches for CR referral, consistently increase the enrolment of patients.[26]

Interestingly the results of this study occurred in an unselected population in which were enrolled also elderly patients including very old patients (>80 years) who received a tailored CR program for their 'fragility', comorbidities, and functional limitations. Furthermore, it has to be noted that hospitalization for cardiovascular cause were reduced in the CR group, thus preventing cardiovascular outcomes and suggesting that CR might reduce also the health care cost. It has been estimated that Cost-effectiveness of CR ranged from an additional US $42 535/quality-adjusted life-year[27] to a reduction of US $650/quality-adjusted life-year for CR compared with control subjects.[28]

Despite these evidences supporting the benefits of CR programs, this service is greatly underutilized, especially by women, elderly, and diabetic patients.[29–31] Referral and participation range between 30% and 50% in Europe and it is around 25% in USA.[12,15] Suaya et al.[13] reported that CR was used in only 14% of elderly patients after ACS and 31% after CABG and less than 30% CR uptake in women are reported by Peek et al.,[32] while in the study of Mezenes et al.[33] only 20% of eligible diabetic patients are referred to CR.

There are several reasons for inadequate use of CR. Firstly, in most of cases patients do not receive appropriate information and encouragement to attend CR by physician and other health professionals; this should be done, as in our study, directly during hospital discharge.

Another important consideration concerns the adherence of the full CR program. It has been demonstrated that 36 sessions of CR are associated with lower risks of death and ACS at 4 years compared with fewer than 36 sessions,[10] but a lot of patients leave the CR program within the first sessions. This event occurs especially in subgroups of high risk patients. Diabetics patients, for example, are less likely to complete the full course of CR compared to non-diabetic individuals (41% vs. 56%; $P < 0.001$) and a meta-analysis revealed a sex difference of 4% (68.6% to 64.2% for men and women, respectively) in adherence to CR programs longer than 12 weeks' duration.

The main consequence is that only few patients reach the targets indicated in the guidelines, as reported in the latest analysis of EUROASPIRE series.[34] In our study, the use of 10 session of 45 min of cyclette training two time a week for 5 weeks, and a second part of 12 session of 45 min of gym training three time a week for 6 weeks with an average duration of the CR program of 5 months has been effective in reducing cardiovascular outcome and may be suggested as a useful approach to adopt. It is important to highlight that in our CR program the supervision of the physical activity required only trained health care professionals that were involved during the physical sessions and a 12-derivations ECG telemetry. This is a simple but efficient methods that can be adopted without the use of expensive resources and can be applied in any ambulatory CR centre.

Novel strategies to promote the use and adherence to CR are now investigated with a greater emphasis on home training in combination with intermittent home visits or telephone conferencing/assessments, or both, to reinforce safety and compliance.[35] Home-based and facility-based programs have shown similar benefits of lowering risk factors, increasing quality of life, and reducing clinical events,[36] but further studies are needed.

Study limitations

Our findings should be interpreted in light of the common limitations of retrospective observational studies; however, the 'Observational Cardiac Rehabilitation Division Registry' was built and prospectively filled in order to periodically evaluate and monitor the epidemiology and the efficacy of the ambulatory CR program. The results of this study derived from a single centre CR program with its own specific CR protocols; however, the CR program in our institution is inspired and follows strictly the international guidelines recommendations.

We did not collect information about adherence on pharmacological therapy; however, despite non-attenders presented at discharged a higher frequency of evidence-based therapy prescription compared to attenders, this was not translated in better outcomes; one could speculate that lower adherence of therapy was present in non-attenders group; however, adherence of therapy was not the aim of our study and further dedicated studies should be performed in the future. An accurate analysis on arrhythmias was not possible; however, a protective role of CR independently from LVEF, and the well-known association between arrhythmias and LVEF in patients with ischaemic cardiomyopathy, makes a relevant and different impact of the arrhythmias between the two groups unlikely. Finally, a number of behavioural factors and attitudes that might affect attendance at CR, data related to socio-economical characteristics of patients and parameters to assess the variation in quality of life were not evaluated.

Conclusions

This study, conducted in a large cohort of patients, demonstrated the positive effects of a modern multidisciplinary CR program in the real world showing a decreased risk of cardiovascular hospitalizations and cardiovascular mortality during a long-term follow-up.

The results of our analysis support the clinical practice guidelines that consider CR an integral part in the treatment of coronary artery disease. All patients should be referred to a CR program after an ACS or coronary revascularization with particular consideration for elderly, diabetics, and women, improving the time of enrolment, accessibility, and adherence to CR.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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