

# Cardiac rehabilitation in chronic heart failure: data from the Italian Survey on cardiac rehabilitation (ISYDE-2008)

Francesco Giallauria<sup>a</sup>, Francesco Fattiroli<sup>b</sup>, Roberto Tramarin<sup>c</sup>, Marco Ambrosetti<sup>d</sup>, Raffaele Griffo<sup>e</sup>, Carmine Riccio<sup>f</sup>, Carlo Vigorito<sup>a</sup>, on behalf of the ISYDE-2008 Investigators of the Italian Association for Cardiovascular Prevention and Rehabilitation (GICR-IACPR)

**Background** Using data from the Italian Survey on cardiac rehabilitation (ISYDE-2008), this study provides insight into the level of implementation of cardiac rehabilitation in patients with chronic heart failure (CHF).

**Methods** Data from 165 Italian cardiac rehabilitation units were collected online from 28 January to 10 February 2008.

**Results** The study cohort consisted of 2281 patients (66.9 ± 11.8 years): 285 (71.3 ± 12.2 years, 66% male) CHF patients and 1996 (66.3 ± 11.6 years, 74% male) non-CHF patients. Compared with non-CHF, CHF patients were older, showed more comorbidity, had lower left ventricular (LV) ejection fraction and reduced access to functional evaluation, underwent more complications during cardiac rehabilitation, and had longer length of in-hospital stay. CHF patients were also more likely to be transferred to ICU (9 versus 3%,  $P < 0.0001$ ), and less likely to be discharged home (85 versus 92%, respectively,  $P < 0.0001$ ). Also, discharge prescriptions were significantly different from those of non-CHF patients. Finally, CHF patients had higher mortality during cardiac rehabilitation (1.7 versus 0.5%,  $P = 0.01$ ). After adjusting for age, ejection fraction, comorbidity, previous interventions and complications during cardiac rehabilitation, multivariate logistic analysis showed that not performing any of the physical performance tests [odds ratio (OR) = 7.0, 95% confidence interval (CI), 1.9–25.8,  $P = 0.003$ ], acute respiratory failure

(OR = 2.3, 95% CI, 1.3–4.1,  $P = 0.002$ ), acute kidney insufficiency or worsening of chronic kidney disease (OR = 2.9, 95% CI, 1.5–5.6,  $P = 0.001$ ) and worsening of cognitive impairment (OR = 3.7, 95% CI, 2.0–6.7,  $P < 0.001$ ) were significant predictors of death in CHF patients.

**Conclusion** The ISYDE-2008 survey provided a detailed snapshot of cardiac rehabilitation in CHF patients, and confirmed the complexity and the more severe clinical course of these patients during cardiac rehabilitation.

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**Keywords:** cardiac rehabilitation, cardiopulmonary exercise testing, cardiovascular morbidity, cardiovascular mortality, chronic heart failure, elderly, exercise training, myocardial infarction, physical performance test

<sup>a</sup>Department of Clinical Medicine, Cardiovascular and Immunological Sciences, Cardiac Rehabilitation Unit, University of Naples 'Federico II', Naples, Italy, <sup>b</sup>Department of Critical Care Medicine and Surgery, Cardiac Rehabilitation Unit, University of Florence and Azienda Ospedaliero-Universitaria Careggi, Florence (FI), Italy, <sup>c</sup>Division of Cardiac Rehabilitation, Fondazione Europea di Ricerca Biomedica, Cernusco S/N (MI), Italy, <sup>d</sup>Clinica 'Le Terrazze', Cunardo (VA), Italy, <sup>e</sup>Department of Cardiology, Cardiac Rehabilitation Unit, La Colletta Hospital, Arenzano (GE), Italy and <sup>f</sup>Azienda Ospedaliera S. Anna e S. Sebastiano di Caserta, Caserta (CE), Italy

Correspondence to Francesco Giallauria, MD, PhD, Department of Clinical Medicine, Cardiovascular and Immunological Sciences, Cardiac Rehabilitation Unit, University of Naples 'Federico II' via Pansini 5, 80131 Naples, Italy  
 Tel: +39(0)817462963; fax: +39(0)817462963; e-mail: giallauria@libero.it

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## Introduction

Chronic heart failure (CHF) is a major public health problem. Currently, more than 15 million patients have heart failure in North America and Europe, with nearly 1.5 million new cases every year.<sup>1,2</sup> Heart failure is the most frequent cause of hospitalization among people older than 65 years of age, and these hospitalizations account for the enormous cost of the disease.<sup>3,4</sup>

A number of prior studies showed positive effects of exercise training on exercise capacity, quality of life and biomarkers, observing relatively few complications during training in CHF patients.<sup>5–7</sup> Two recent meta-analyses and a randomized-controlled trial suggested improved survival and decreased hospitalizations for

CHF patients undergoing exercise training as compared with a nonexercising control group.<sup>8–10</sup>

In 2006, the Italian National System for Guidelines of the Italian Health Ministry published the Guidelines on Cardiac Rehabilitation and Secondary Prevention, with the endorsement of the Italian Agency of Regional Health Systems.<sup>11</sup> Although the adherence to Guidelines has been shown to be associated with improved outcomes, their current implementation in Italy, as in other European countries, remains frequently defective.<sup>12–16</sup> In the recent past, the Italian Association for Cardiovascular Prevention and Rehabilitation [Gruppo Italiano di Cardiologia Riabilitativa (GICR)-IACPR] promoted and carried out a detailed observational study of cardiac

rehabilitation programs available in Italy.<sup>17</sup> The broad participation of cardiac rehabilitation centers throughout Italy and the dimension of surveyed population proved to represent the real, pragmatic rehabilitation world and to describe the clinical profile of patients referred to cardiac rehabilitation programs.

As a considerable part of this study cohort consisted of CHF patients, the present survey aimed at providing an insight into the clinical characteristics and course of a CHF population in the real world of cardiac rehabilitation in Italy.

## Methods

### Study design

The multicenter, prospective observational study design of the Italian Survey on cardiac Rehabilitation (ISYDE-2008) has been described in detail elsewhere.<sup>14,17</sup> In summary, the primary purpose of the ISYDE-2008 study was to take a snapshot of the current organization, settings and provision of cardiac rehabilitation in Italy and to describe the patient population referred to cardiac rehabilitation, giving a comprehensive and detailed description of clinical characteristics, risk profile, diagnostic procedures, exercise and educational program, discharge modalities, treatment at discharge and follow-up schedules. The enrollment period lasted from 28 January to 10 February 2008. Data were collected on a web-based Case Report Form, which collected data on clinical characteristics, diagnostic procedures, exercise and educational programs, treatment and follow-up plans of all the consecutive patients discharged from cardiac rehabilitation programs in the 2-week study period. The present study focuses on patients entering cardiac rehabilitation with an admitting diagnosis of CHF. Cognitive function was evaluated by Mini-Mental State Evaluation (MMSE),<sup>18</sup> and cognitive impairment was assigned when corrected MMSE value was less than 21.

### Participating centers

The survey was designed to be carried out in all Italian residential or outpatient cardiac rehabilitation centers. Centers were invited to participate in the survey on a purely voluntary basis by the executive board of the study and by the regional GICR-IACPR coordinator, who was responsible for interfacing with the investigators in each of the participating centers and overlooked the implementation of the survey protocol. On the basis of information collected from previous surveys and registries and through an active search of National Health System authorized facilities carried out at regional level, 208 facilities were identified as potential providers of cardiac rehabilitation programs and were invited to participate in the study. However, 18 centers were found to be inactive or still in a preoperational phase at the time of the study, whereas 25 (13% of the remaining 190) were unwilling or unable to participate. Thus, data collected in the study

refer to 165 cardiac rehabilitation units (87% of all invited facilities). These cardiac rehabilitation units, representative of national cardiac rehabilitation organization, were subdivided into 103 (62.4%) residential units, 18 (10.9%) facilities with day-hospital care, and 33 (20%) facilities with outpatient cardiac rehabilitation [information not available in 11 cardiac rehabilitation units (6.7%)]. The complete list of ISYDE-2008 investigators and participating centers is reported in the Acknowledgements.

### Role of the funding source

No funding sources had any role in the study design, conduction, data collection, analysis, data interpretation or writing of this report. The GICR-IACPR coordinated the study, managed the data and undertook all analyses. All members of the scientific board and writing committees had full access to the database and assumed final responsibility for the results submitted for publication.

### Statistical analysis

The main analysis was performed subdividing the study cohort into two groups, according to the diagnosis of CHF. Data are expressed as means  $\pm$  SD or proportions. Comparisons between groups were performed by unpaired *t* test,  $\chi^2$  or Fisher exact test as required. Correlations between variables were assessed with Pearson's correlation coefficient. Predictors of death were evaluated with multivariate logistic regression analysis. All analyses were performed using SAS (Version 9.1, SAS Institute Inc., Cary, North Carolina, USA) with significance set at  $P < 0.05$ .

## Results

The entire ISYDE study cohort consisted of 2281 patients ( $66.9 \pm 11.8$  years): 285 CHF patients (age  $71.3 \pm 12.2$  years, 66% male) and 1996 non-CHF patients (age  $66.3 \pm 11.6$  years, 74% male). Table 1 summarizes the demographic and risk profile characteristics of the study population. Patients were subdivided in a low, medium or high-risk score according to the number of cardiovascular risk factors present. CHF patients showed a significantly higher cardiovascular risk factor score (including smoking, history, hypertension, dyslipidemia, obesity, diabetes, sedentary lifestyle and early menopause) compared with non-CHF patients ( $P = 0.04$ ).

**Table 1 Demographic and risk profile characteristics of the study population (n, %)**

	CHF (n = 285)	Non-CHF (n = 1996)	P
Age (years) (mean $\pm$ SD)	71.3 $\pm$ 12.2	66.3 $\pm$ 11.6	<0.0001
Sex (Male)	189 (66.3)	1488 (74.5)	0.003
Cardiovascular risk factors <sup>a</sup>			
0–2 (low)	107 (37.6)	804 (40.3)	0.04
3–5 (medium)	140 (49.1)	1019 (51.0)	
>5 (high)	38 (13.3)	173 (8.7)	

CHF, chronic heart failure. <sup>a</sup>Smoking, family history of early coronary heart disease, high blood pressure, hypercholesterolemia, BMI more than 27 kg/m<sup>2</sup>, diabetes, sedentary lifestyle, early menopause.

**Table 2 Comorbidity in patients admitted to cardiac rehabilitation program (n, %)**

	CHF (n = 285)	Non-CHF (n = 1996)	P
Previous myocardial infarction	93 (32.6)	410 (20.5)	<0.0001
Previous percutaneous transluminal coronary angioplasty	44 (15.4)	181 (9.1)	0.0007
Previous cardiac surgery	81 (28.4)	169 (8.5)	<0.0001
Carotid arteries atherosclerosis <sup>a</sup>	24 (8.4)	136 (6.8)	0.32
Symptomatic peripheral artery disease <sup>b</sup>	31 (10.9)	120 (6.0)	0.002
Chronic obstructive pulmonary disease	40 (14.0)	72 (3.6)	<0.0001
Chronic kidney disease <sup>c</sup>	69 (24.2)	131 (6.6)	<0.0001
Stroke	15 (5.3)	68 (3.4)	0.11
Cognitive impairment	15 (5.3)	49 (2.4)	0.007
Gastroesophageal disease	15 (5.3)	103 (5.2)	0.94
Diabetes	94 (33.0)	381 (19.1)	<0.0001
Cancer	20 (7.0)	63 (3.2)	0.001
Orthopedic/joints/immune-related disease	46 (16.1)	161 (8.1)	<0.0001

CHF, chronic heart failure. <sup>a</sup>Stenosis more than 70% or previous revascularization. <sup>b</sup>Fontaine stage more than 1 or previous revascularization. <sup>c</sup>Creatinine at least 1.5 mg/dl.

Compared with non-CHF, CHF patients showed a greater frequency of comorbidities such as previous acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), cardiac surgery, peripheral artery disease (PAD), chronic obstructive pulmonary disease (COPD), cognitive impairment, cancer and orthopedic/joints/immune-related diseases (Table 2).

During cardiac rehabilitation programs, a higher percentage of CHF patients developed complications such as severe ventricular arrhythmias and acute kidney disease or worsening of chronic kidney disease (CKD), and required inotropic support or respiratory assistance: these were also the more frequent complications during the cardiac rehabilitation program, apart from anemia and atrial fibrillation, which, however, were equally observed in CHF and non-CHF patients (Table 3).

Differences between CHF and non-CHF patients were also detected in the access to diagnostic procedures and interventions during cardiac rehabilitation. Compared with non-CHF, CHF patients more likely underwent diagnostic procedures such as 6-minute walking test

(6MWT) and cardiopulmonary stress testing on admission or at discharge (Table 4). However, as many as 75 CHF patients (26%) received no physical performance test (6MWT, exercise stress testing or cardiopulmonary exercise testing); this proportion was significantly greater than in non-CHF patients (20%,  $P < 0.0001$ ). Compared with non-CHF not performing any physical performance testing (20% of the non-CHF cohort), CHF patients not performing any physical performance testing (26% of the CHF cohort) showed a higher percentage of coexisting comorbidities such as previous AMI (32 versus 17%,  $P = 0.002$ ), PAD (15 versus 6%,  $P = 0.004$ ), COPD (24 versus 14%,  $P = 0.03$ ), CKD (33 versus 13%,  $P < 0.0001$ ), cancer (11 versus 3%,  $P = 0.003$ ), and orthopedic disease (24 versus 14%,  $P = 0.03$ ), or previous interventions such as cardiac surgery (24 versus 9%,  $P = 0.0001$ ) or PCI (14 versus 5%,  $P = 0.003$ ), respectively; these patients also showed a higher percentage of complications during the cardiac rehabilitation program such as severe ventricular arrhythmias (11 versus 1%,  $P < 0.0001$ ) and kidney failure (17 versus 5%,  $P = 0.0002$ ). Finally, not undergoing any physical performance test

**Table 3 Complications during cardiac rehabilitation programs (n, %)**

	CHF (n = 285)	Non-CHF (n = 1996)	P
Atrial fibrillation	29 (10.2)	173 (8.7)	0.40
Severe ventricular arrhythmias <sup>a</sup>	16 (5.6)	27 (1.3)	<0.0001
Definitive pacemaker implantation	5 (1.7)	8 (0.4)	0.004
Acute myocardial infarction	1 (0.3)	9 (0.4)	0.81
Cerebrovascular events <sup>b</sup>	3 (1.0)	12 (0.6)	0.37
Worsening of cognitive impairment	7 (2.5)	36 (1.8)	0.44
Anemia <sup>c</sup>	16 (5.6)	145 (7.3)	0.31
Acute renal failure or worsening of CKD <sup>d</sup>	25 (8.8)	46 (2.3)	<0.0001
Sternal revision	0 (0)	7 (0.4)	0.25
Massive pleural effusion needing thoracentesis	3 (1)	29 (1.5)	0.59
Inotropic support/mechanical assistance	14 (4.9)	9 (0.4)	<0.0001
Acute respiratory insufficiency requiring assistance <sup>e</sup>	13 (4.6)	28 (1.4)	0.0002
Systemic infections	7 (2.5)	60 (3.0)	0.61
Blood transfusions	21 (1.2)	10 (1.8)	0.34
Death	5 (1.7)	10 (0.5)	0.01

CHF, chronic heart failure; CKD, chronic kidney disease. <sup>a</sup>More than 30 s or symptomatic ventricular tachycardia. <sup>b</sup>Stroke, Transient Ischemic Attack. <sup>c</sup>Hb 10 g/dl or less, or at least 3 g/dl reduction with respect to the preindex event value. <sup>d</sup>Creatinine at least 2.5 mg/dl when preindex event value less than 1 mg/dl or creatinine increase at least 1 mg/dl in patients with previous chronic kidney disease. <sup>e</sup>including oxygen therapy, mechanical ventilation, continuous positive airway pressure (cPAP), Bilevel Positive Airway Pressure (biPAP) more than 96 h.

**Table 4 Diagnostic and therapeutic procedures during cardiac rehabilitation programs (n, %)**

	CHF (n = 285)	Non-CHF (n = 1996)	P
6-Minute walking test on admission	145 (51)	838 (42)	0.005
6-Minute walking test at discharge	147 (51.6)	800 (40.1)	0.002
Exercise stress testing on admission	7 (2.5)	439 (22)	<0.0001
Exercise stress testing at discharge	19 (6.7)	686 (34.4)	<0.0001
Cardiopulmonary exercise stress testing on admission	26 (9.1)	96 (4.8)	0.002
Cardiopulmonary exercise stress testing at discharge	56 (19.6)	101 (5.1)	<0.0001
No physical performance test at all	75 (26)	413 (20)	<0.0001
Echocardiography	272 (95)	1824 (91)	<0.0001
Holter Electrocardiogram	146 (51.2)	774 (38.8)	<0.0001
Venous infusions	68 (23.9)	171 (8.6)	<0.0001
Geriatric multidimensional evaluation	96 (33.7)	358 (17.9)	<0.0001
Computed tomography	13 (4.6)	76 (3.8)	0.54
Ultrasounds	50 (17.5)	324 (16.2)	0.57
Group exercise sessions	198 (69.5)	1597 (80.0)	<0.0001
Individual exercise sessions	109 (38.2)	478 (23.9)	<0.0001

CHF, chronic heart failure.

was a significant predictor of death during cardiac rehabilitation in CHF patients [odds ratio (OR) 7.0, 95% confidence interval (CI), 1.9–25.8,  $P=0.003$ ].

Echocardiography showed a lower percentage of CHF patients with preserved left ventricular ejection fraction (LVEF >50%), compared with non-CHF patients (23 versus 73%,  $P<0.0001$ , respectively); and a higher percentage of moderate (LVEF = 30–49%, 47 versus 24%,  $P<0.0001$ , respectively) and severe (LVEF < 30%, 30 versus 3%,  $P<0.0001$ , respectively) LV systolic dysfunction.

Compared with non-CHF, CHF patients were more frequently discharged on angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB), nitrates, diuretics, oral anticoagulant therapy, digitalis, amiodarone, insulin and heparin, and less frequently on statin and aspirin (Table 5). No significant changes were observed in  $\beta$ -blocker prescription (Table 5).

CHF patients had a significantly longer hospital length of stay ( $20 \pm 13$  versus  $18 \pm 10$  days,  $P=0.003$ ), less daily

access to hospital daycare ( $13 \pm 11$  versus  $16 \pm 9$  days,  $P=0.04$ ), were less likely to be discharged home (85 versus 92%,  $P<0.0001$ ), and rather more likely transferred to ICU (9 versus 3%,  $P<0.0001$ ) compared with non-CHF patients, respectively.

CHF patients had a higher death rate during cardiac rehabilitation programs (1.7 versus 0.5%,  $P=0.01$ ). After adjusting for age, ejection fraction, preexisting comorbidities or previous interventions (AMI, PCI, cardiac surgery, carotid artery critical lesions, PAD, COPD, CKD, stroke, cognitive impairment), complications during the cardiac rehabilitation program (atrial fibrillation, severe ventricular arrhythmias, acute respiratory insufficiency and acute renal failure or worsening of CKD) and not performing any physical performance testing (6MWT, exercise stress testing or cardiopulmonary exercise testing), multivariate logistic analysis showed that acute respiratory insufficiency (OR 2.3, 95% CI, 1.3–4.1,  $P=0.002$ ), acute kidney insufficiency or worsening of CKD (OR 2.9, 95% CI, 1.5–5.6,  $P=0.001$ ), worsening of cognitive impairment (OR 3.7, 95% CI, 2.0–6.7,  $P<0.001$ ), severe ventricular

**Table 5 Drug therapy at hospital discharge after cardiac rehabilitation programs**

	CHF (n = 285)	Non-CHF (n = 1996)	P
Angiotensin-converting enzyme inhibitors	180 (63.2)	1077 (54.0)	0.003
Angiotensin II receptor blockers	68 (23.9)	319 (16.0)	0.001
$\beta$ -Blockers	190 (66.7)	1376 (68.9)	0.44
Nitrates	90 (31.6)	350 (17.5)	<0.0001
Diuretics	249 (87.4)	919 (46.0)	<0.0001
Statins	155 (54.4)	1355 (67.9)	<0.0001
Fibrates	2 (0.7)	6 (0.3)	0.28
Omega-3 fatty acids	56 (19.6)	322 (16.2)	0.13
Oral anticoagulant therapy	97 (34)	507 (25.4)	0.002
Aspirin	136 (47.7)	1372 (68.7)	<0.0001
Digitalis	58 (20.3)	66 (3.3)	<0.0001
Amiodarone	58 (20.3)	74 (3.7)	<0.0001
Calcium channel blockers	45 (15.8)	391 (19.6)	0.13
Insulin	50 (17.5)	161 (8.1)	<0.0001
Oral hypoglycemic drugs	49 (17.2)	304 (15.2)	0.39
Antidepressant	22 (7.7)	119 (6.0)	0.25
Antiarrhythmics	6 (2.1)	35 (1.7)	0.67
Heparin	15 (5.2)	39 (2.0)	0.0006

CHF, chronic heart failure.

arrhythmias (OR 9.8, 95% CI, 2.0–48.6,  $P=0.005$ ), and not performing any of the physical performance tests (OR 7.0, 95% CI, 1.9–25.8,  $P=0.003$ ) were significant predictors of death in CHF patients.

## Discussion

The present study, by deriving data from the 2008 ISYDE survey, is the first to explore in such depth the characteristics of the ‘real world’ CHF patients admitted to cardiac rehabilitation programs in Italy.

Although exercise-based cardiac rehabilitation is recognized as an essential component in the contemporary management of patients with CHF, including the elderly, admission to cardiac rehabilitation and secondary prevention programs of patients with CHF is far from optimal.<sup>14–16</sup> The present survey revealed that only 12.5% of patients admitted to cardiac rehabilitation had a diagnosis of CHF. These patients were older, more frequently men and with more severe comorbidities, thus, closely reflecting the real world of patients with CHF presenting in the acute ward. As expected, we found higher mean age in CHF patients (127 out of 285 CHF patients were  $\geq 75$  years old), as the increased severity and complexity of cardiac disease in older patients, associated with higher frequency of comorbidities (particularly COPD and renal insufficiency) may easily lead to CHF and precipitate an acute episode of heart failure.<sup>19</sup> In line with previous findings,<sup>20</sup> this survey confirmed in CHF patients the large burden of comorbidities (previous coronary event and revascularizations, CKD, COPD, diabetes, cancer and orthopedic diseases) explaining the higher frequency of complications occurring during cardiac rehabilitation in this patient population.

In particular, CHF patients participating to cardiac rehabilitation programs had a higher prevalence of COPD compared with non-CHF patients (14 versus 3.6%,  $P<0.0001$ ). Concomitant COPD has an important impact on mortality and hospitalization rates as well as on quality of life in patients with CHF.<sup>21</sup> Multiple common mechanisms may explain this negative prognostic association, such as exercise-induced increase in functional residual capacity,<sup>22</sup> COPD induced hemoglobin desaturation hypoxemia or further worsening of right-ventricular function,<sup>23</sup> or activation of inflammatory mechanisms.<sup>24</sup>

In fact, in the present survey, COPD strongly increases the burden of care in patients with heart failure: the association of COPD with CHF was likely responsible for the higher frequency of respiratory assistance in CHF (4.6 versus 1.4%,  $P=0.0002$ ); and, in addition, acute respiratory insufficiency was a significant predictor of death in CHF patients during cardiac rehabilitation (OR 2.3, 95% CI, 1.3–4.1,  $P=0.002$ ).

This survey also highlighted the higher prevalence of diabetes in CHF patients participating in cardiac

rehabilitation programs, compared with non-CHF patients (33 versus 19%,  $P<0.0001$ , respectively). Diabetes mellitus is indeed a well-known risk factor for heart failure. Even after adjustment for concomitant risk factors, diabetic patients have an almost two-fold increased risk of heart failure.<sup>25</sup> Previous data showed that the prevalence of concomitant diabetes mellitus in patients with heart failure varies from 19 to 31%.<sup>26</sup> The strong association between diabetes mellitus and heart failure is partly explained by the high prevalence of ischemic heart disease, hypertension and obesity in diabetic patients. The associated increase in advanced glycosylation end products, endothelial dysfunction, increased circulating free fatty acids, a preferential shift in myocardial metabolism toward less efficient fatty acid oxidation, and a proinflammatory state may all contribute to the development of myocardial dysfunction, reduced exercise tolerance and heart failure.<sup>27</sup>

Compared with the non-CHF cohort, CHF patients also showed a higher prevalence of CKD (24.2 versus 6.6%,  $P<0.0001$ ), and acute kidney failure or worsening of CKD was a significant predictor of death in CHF patients during cardiac rehabilitation programs (OR 2.9, 95% CI, 1.5–5.6,  $P=0.001$ ). Renal dysfunction is a common feature in CHF patients and the definition of ‘cardio-renal syndrome’ is used to describe the concomitant presence of renal and cardiac dysfunction.<sup>28</sup> Renal dysfunction and heart failure share some comorbidity such as hypertension, diabetes and CAD, which confer a significantly increased risk of developing both conditions. They also share common pathophysiological mechanisms, including neurohormonal and inflammatory activation; in addition, several drugs frequently used in CHF patients, such as diuretics, ACE-I or ARBs might impair kidney function in CHF patients and lead to acute renal function deterioration.<sup>29</sup> Therefore, these observations suggest the need to monitor renal function closely in patients with CHD during the cardiac rehabilitation protocol.

The present survey showed that the diagnosis of cognitive impairment was significantly more frequent in CHF patients as compared to the non-CHF cohort, a likely consequence of the more advanced age of our CHF population. Cognitive dysfunction and heart failure are commonly associated conditions in the elderly.<sup>30,31</sup> On the contrary, previous studies showed that the risk of cognitive impairment is increased in CHF patients, as compared to the general population, independently of age of the patient.<sup>30,31</sup> Potential underlying mechanisms for cognitive dysfunction in heart failure may involve low cardiac output status with consequent cerebral hypoperfusion as well an intrinsic increased risk of cerebrovascular ischemic events.<sup>30,31</sup> Therefore, these findings suggest that an initial evaluation of cognitive performance should be implemented in CHF patients admitted to cardiac rehabilitation. Of note, worsening of cognitive

impairment was a significant predictor of death in the CHF cohort.

Compared with the non-CHF cohort, functional evaluation tests such as 6MWT and cardiopulmonary exercise stress test were more frequently performed in CHF patients, the former as a submaximal test in patients not capable of exercising on a cycle or treadmill, the second in a small proportion of less functionally compromised patients. However, compared with non-CHF, a larger proportion of CHF patients did not perform cycle or treadmill exercise stress test or any type of physical performance test at all (26 versus 20%,  $P < 0.0001$ ). Interestingly, not performing any physical performance testing was a significant predictor of death in CHF patients (OR 7.0, 95% CI, 1.9–25.8,  $P = 0.003$ ). These findings might reflect a more compromised cardiovascular status preventing CHF patients from performing exercise stress testing, or might be due to the more frequent comorbidities with relative contraindication to exercise (COPD, orthopedic-joints disease etc.).

The present survey also revealed interesting differences in prescription of drugs at discharge. CHF patients were discharged from Cardiac Rehabilitation Units with fewer indications to statins, compared with the non-CHF cohort, thus, confirming the difficulties of adopting in the real clinical world and in CHF patients the recommendations of international guidelines regarding secondary prevention.<sup>15</sup> As expected, CHF patients received at discharge more frequent prescriptions of ACE-I, ARBs, digitalis and nitrates. Amiodarone and insulin were more prescribed for supraventricular or ventricular arrhythmias and diabetes, respectively. The low aspirin prescription was, at least in part, a reflection of the increased combined prescription of oral anticoagulants and heparin.

Finally, mortality during the performance of cardiac rehabilitation program was higher in CHF patients compared with the non-CHF cohort (1.7 versus 0.5%,  $P = 0.01$ ), reflecting the higher clinical risk profile of these patients. Unfortunately, we do not have a control group of patients with CHF not entering in cardiac rehabilitation to adequately evaluate the significance of this finding. However, the mortality in the first months following hospital discharge of CHF patients not enrolled in cardiac rehabilitation protocols is likely to be even higher than that observed in our study.<sup>32</sup>

#### Study limitations

The number of patients with CHF reported in the present survey is very small (about 12% of the overall population). This makes the study underpowered for a deepened interpretation. This probably depends on the very small time of the enrollment period (only 2 weeks). The combination of data from cardiac rehabilitation centers offering very different cardiac rehabilitation regimens (e.g. residential versus outpatients) is another

confounder. The observational nature of the study cannot rule out that the more severely compromised patients with CHF were not addressed to cardiac rehabilitation, and therefore those described in our study may represent a selected, more relatively healthy minority. However, this survey successfully highlighted crucial differences in the clinical characteristics, risk profile, management and short-term outcome in a CHF patient population entering cardiac rehabilitation programs in Italy, compared with non-CHF patients. Another putative limitation of the present study was the lack of reporting some important functional and clinical parameters of possible interest; this was due to the short-term survey characteristics of the study, which collected the essential data in order to characterize the demographic and clinical course of the patients. Finally, according to recent evidence,<sup>33–35</sup> the present survey did not collect data regarding modality of exercise training regimen (interval versus continuous) or the dose of exercise (in terms of volume and intensity) which can greatly affect the functional and clinical parameters (together with outcome) of CHF patients.

In conclusion, this survey shows in a large population the characteristics of the clinical risk profile, resource utilization, pharmacologic treatment and course of cardiac rehabilitation programs in CHF patients entering cardiac rehabilitation programs in Italy. Future studies are needed in order to identify the best strategies for expanding referral to cardiac rehabilitation of CHF patients, particularly of those more compromised, and fostering the application of tailored functional evaluation, educational intervention, optimization of pharmacological and nonpharmacological treatment, and adherence to secondary prevention guidelines, with the aim of reducing in-hospital complications and improving functional recovery, long-term mortality, morbidity and quality of life of these high-risk patients.

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##### ISYDE-2008 Study Investigators

Scientific Board: R. Tramarin (Cernusco S/N–MI), R. Griffo (Arenzano–GE), C. Riccio (Caserta), R. Carlon (Cittadella - PD), A. Castello (Palermo), M. Ferratini (Milano), C. Schweiger (Milano), C. Chieffo (Napoli), C. Vigorito (Napoli).

Writing Committee: R. Tramarin (Cernusco S/N–MI), C. Vigorito (Napoli); M. Ambrosetti (Cunardo–VA), S. De Feo (Peschiera del Garda–VR), R. Griffo (Arenzano–GE), M. Piepoli (Piacenza), C. Riccio (Caserta).

Executive Committee: M. Ambrosetti (Cunardo – VA), S. De Feo (Peschiera del Garda – VR), T. Diaco (Rivolta d'Adda – CR).

Delegati Regionali del Gruppo Italiano di Cardiologia Riabilitativa e Preventiva: Abruzzo: C. Ciglia (Chieti),

Basilicata: A. Lapolla (Policoro - MT), Calabria: F. Pietropaolo (Soriano Calabro - VV), Campania: G. Furgi (Telese Terme - BN), Friuli Venezia Giulia: G. Martin (Sacile - PN), Emilia Romagna: P. Semprini (Rimini), Lazio: A. Avallone (Roma), Liguria: D. Bertoli (Sarzan - SP), Lombardia: T. Diaco (Rivolta d'Adda - CR), Marche: R. Belardinelli (Ancona), Piemonte: F. Soffiantino (Lanzo Torinese - TO), Puglia: D. Scrutinio (Cassano Murge - BA), Sardegna: P. Maxia (Cagliari), Sicilia: R. Coco (Catania), Toscana: C. Giustarini (Volterra - PI), Umbria: P. Anniboletti (Perugia), Veneto: G. Favretto (Motta di Livenza - TV).

Technical Support: P. Vaghi (Saronno), P. Calisi (Arenzano - GE), C. Chiavetta (Genova), Aristeia S.p.A. (Genova), Segno & Forma S.p.A. (Milano)

### ISYDE-2008 Investigators

(Italian Regions in bold)

**Abruzzo:** Leonello Guarracini - Presidio Ospedale Tagliacozzo - Tagliacozzo; Carlo Ciglia - Casa di Cura Villa Pini D'Abruzzo - Chieti; Giorgio Marcellini - Presidio Ospedaliero S. Omero - S. Omero. **Calabria:** M. Iannopolo - Presidio Ospedaliero Siderno - USL 9 Locri (RC) - Siderno; Gennarino Borrello - Azienda Ospedaliera Mater Domini - Catanzaro; Milena Matta - Presidio Ospedaliero di Cetraro - Cetraro; N. Peccerillo - Ospedale di Mormanno - ASL 2 Castrovillari - Mormanno; Franco Boncompagni - Ospedale dell'Annunziata - Cosenza; Achille Amici - Casa di Cura 'San Francesco' - Mendicino (CS) - Mendicino; Francesco Pietropaolo - Presidio Ospedaliero - Soriano Calabro; Emidio Feraco - IRCCS INRCA - Cosenza; G. Pulitano - Presidio Ospedaliero Policlinico Madonna della Consolazione - Reggio Calabria; Ermete Tripodi - ASP 5 Regione Calabria - Scilla. **Campania:** Giuseppe Furgi - IRCCS Fondazione Salvatore Maugeri - Telese Terme; Carmelo Chieffo - Casa di Cura Clinical Center - Napoli; Soccorso Capomolla - Presidio Ospedaliero Polispecialistico Don Gnocchi Onlus - Sant'Angelo dei Lombardi; Paolo Golino - Azienda Ospedaliera di Caserta - Dipartimento di Cardiologia - Caserta; Genaro Parrilli - Campolongo Hospital S.p.A. Casa di Cura - Eboli; Antonio Di Patria - Casa di Cura Villa delle Magnolie - Castel Morrone; Claudio Di Gioia - Casa di Cura Privata Villa Margherita, Istituto S. Giuseppe Moscati - Benevento; Domenico Micieli - Azienda Ospedaliera V. Monaldi - Napoli; Carlo Vigorito - Azienda Universitaria Policlinico - Università di Napoli Federico II - Napoli; Silvio Perrotta - ASL Napoli 1 - Napoli; Alessandro Rubino - Azienda S. G. Moscati - Avellino; Vincenzo Aulitto - Centro Serapide S.p.A. - Pozzuoli; Gerardo Riccio - Ospedale di Nocera - Nocera Inferiore. **Emilia Romagna:** Luciano Codec - Azienda Universitaria Ospedale S. Anna - Ferrara; Paolo Coruzzi - Fondazione Don Carlo Gnocchi - Onlus - Parma; Enrico Violi - Azienda Ospedaliera di Reggio Emilia -

Castelnuovo Monti; Massimo Nardini - Ospedale Regina Margherita - Castelfranco Emilia; Stefano Urbinati - Azienda USL di Bologna - Bologna; Sylvia Cruz - Casa di Cura Privata ad Indirizzo Riabilitativo San Giacomo srl - Ponte dell'Olio; Pierluigi Semprini - Ospedale Infermi Rimini - Rimini; Massimo Piepoli - Azienda Unità Sanitaria Locale di Piacenza - Piacenza; Alessandro Fucili - Ospedale Sant'Anna - Ferrara; Massimo Cerulli - Ospedale Privato Accreditato Villa Pineta - Gaiato di Pavullo N/F; Bini Roberto - Azienda USL Cesena - Cesenatico; Guido Balestra - Villa Maria Cecilia Hospital - Cotignola. **Friuli Venezia Giulia:** Dulio Tuniz - IMFR Udine - ASS N. 4 - Udine; Giovanni Martin - Azienda Ospedaliera Santa Maria degli Angeli Pordenone - Sacile; Pierpaolo Gori - Casa di Cura Pineta del Carso - Aurisina; Roberto Marini - ASS N. 2 Isontina - Gorizia; Tullio Morgera - Ospedale San Polo - Monfalcone. **Lazio:** Franco Di Mario - Istituto Clinico Riabilitativo Villa delle Querce - Nemi; Maurizio Volterrani - IRCCS San Raffaele Pisana - Roma; Alfonso Galati - Presidio Ospedaliero Santo Spirito, Presidio Villa Betania, ASL Roma E - Roma; Alessandro Salustri - Policlinico Luigi Di Liegro - Roma; Anna Patrizia Jesi - Presidio Ospedaliero Salus Infirmorum - Roma; Augusto Lacch - Azienda Ospedaliera San Camillo - Forlanini - Roma; Francesco Loperfido - Complesso Integrato Columbus. Università Cattolica del Sacro Cuore - Roma. **Liguria:** Luca Corsiglia - Istituto Cardiovascolare Camogli - Ruta di Camogli; Raffaele Griffo - ASL 3 Genovese - Arenzano; Paolo Pantaleo - Struttura Ospedaliera Privata Accreditata Villa Azzurra - Rapallo; Guido Gigli - Regione Liguria ASL 4 - Centro Regionale di Riabilitazione Cardiologica - Sestri Levante; Daniele Bertoli - ASL 5 Spezzino - Sarzana. **Lombardia:** Diego Marchesi - Clinica Domus Salutis Ancelle della Carità - Brescia; Oreste Febo - IRCCS Fondazione Salvatore Maugeri - Montescano; Franco Cobelli - IRCCS Fondazione Salvatore Maugeri Pavia - Pavia; Claudio Malinverni - Azienda Ospedaliera 'Bolognini' - Sariate; Maurizio Ferratini - Fondazione Don Gnocchi Onlus - Milano; Norman Jones - Ospedale Trabattoni Ronzoni - Seregno; Claudio Anzà - Multimedita Holding - Presidio Ospedaliero di Castellanza - Castellanza; R. Frizzelli - Azienda Ospedaliera C. Poma di Mantova - Bozzolo; Paolo Gei - Spedali Civili di Brescia - Gardone Riviera; Flavio Acquistapace - Policlinico di Monza - Monza; Roberto Pedretti - IRCCS Fondazione Salvatore Maugeri - Tradate; Roberto Tramarin - Fondazione Europea di Ricerca Biomedica - Onlus - Cernusco S/N - Milano; Stefano Carugo - Centro di Cardiologia Riabilitativa - Pio Albergo Trivulzio - Milano; Gabriella Malfatto - Istituto Auxologico Italiano IRCCS - Milano; Tommaso Diaco - Azienda Ospedale Maggiore di Crema - Rivolta D'Adda; Marco Ambrosetti - Clinica Le Terrazze - Cunardo; Carlo - Meloni - Ospedale San Raffaele IRCCS U.O. Riabilitazione Cardiaca - Milano; Amerigo Giordano - IRCCS Fondazione

Salvatore Maugeri – Lumezzane; Alberto Schizzarotto - Azienda Ospedaliera S. Antonio Abate di Gallarate - Somma Lombardo; Renzo Zanettini - Azienda Ospedaliera Istituti Clinici di Perfezionamento – Milano; Roberto Bosco - Ospedale Romano di Lombardia - Romano di Lombardia; Giuseppe Occhi - Azienda Ospedaliera della Valtellina e Valchiavenna – Sondalo; Stefano Aglieri - Istituto Clinico Humanitas – Rozzano; Giuseppe Caprioli - Humanitas - Cliniche Gavazzeni S.p.A. – Bergamo; Nicola Cuocina - Azienda Ospedaliera Ospedali Riuniti di Bergamo – Bergamo; Luciano Lazzaroni, Aurelio Lorenzi - Centro di Cardiologia Riabilitativa di Cesano Boscone - Casa di Cura Ambrosiana - Cesano Boscone; Cinzia Savonelli - Cof Lanzo Hospital S.p.A. Clinica Ortopedica e Fisiatrica. - Lanzo D'Intelvi; Marco Veniani - Azienda G. Salvini Garbagnate Milanese – Rho; Giovanni Corda - Azienda Ospedaliera ed Universitaria: Ospedale di Circolo ed Università dell'Insubria - Varese - Cuasso al Monte; Claudia Meinecke - Azienda Istituti Ospitalieri di Cremona – Cremona; Giuseppe Castiglioni - ASL Prov. Milano - Presidio Ospedaliero Cassano D'Adda - Cassano D'Adda; Ravizza Pierfranco - Azienda Ospedaliera Ospedale di Lecco – Merate; Paolo Giani - Fondazione Europea di Ricerca Biomedica Onlus – Trescore Balneario; Fabio Robustelli della Cuna - Ospedale di Morbegno - ASL Provincia di Sondrio – Morbegno; Giuseppe Gullace - Azienda Provinciale Ospedale di Lecco – Lecco; Federico Passoni – Azienda Ospedaliera di Legnano – Cuggiono; Maria Vittoria Barelli - Centro Fisioterapico Riabilitativo Club Francesco Conti – Milano; Italo Richichi – Ospedale San Matteo U.O. di Riabilitazione – Belgioioso; Angelo Rossi - Casa di Cura Villa Esperia – Salice Terme; Alessandro Politi - Ospedale Generale di Zona – Gravedona. **Marche:** Romualdo Belardinelli - Azienda Ospedaliero - Universitaria Umberto I – Ancona; Casa di Cura Villa Serena – Jesi; Mauro Persico - ASUR Marche Zona Territoriale 12, San Benedetto del Tronto - Area Vasta N. 5 - San Benedetto del Tronto. **Piemonte e Valle d'Aosta:** Pantaleo Giannuzzi - IRCCS Fondazione Salvatore Maugeri, Clinica del Lavoro e della Riabilitazione – Veruno; Gianmauro Mazzucco - Casa di Cura Villa Serena - Centro Medico di Riabilitazione Cardiologica e Pneumologica – Piossasco; Enzo Bosimini - Casa di Cura Major - Sede Distaccata IRCCS Fondazione Maugeri Veruno – Torino; Giuseppe Riva - Casa di Cura Riabilitativa Stella del Mattino – Boves; Francesco Soffiantino - Presidio Ospedaliero di Lanzo - Lanzo Torinese; Nicola Massobrio - Ospedale Evangelico Valdese di Torino – Torino; Luca Gondoni - Unità Operativa ad indirizzo Cardiologico - IRCCS Istituto Auxologico Italiano - Piancavallo di Oggebbio; Franco Aina - Azienda Ospedaliero-Universitaria Ospedale Maggiore della Carità di Novara – Novara; Biagio Ingnoli - Ospedale Ss Trinità – Fossano; Maria Vincenza Cal - Ospedale di Acqui Terme - Acqui Terme; Aillon Costante - Azienda USL Valle D'Aosta - Ospedale Regionale 'Umberto Parini' – Aosta. **Puglie:** Domenico Scrutinio - IRCCS

Fondazione Salvatore Maugeri - Cassano Murge; Massimo Villella - IRCCS Casa Sollievo della Sofferenza - San Giovanni Rotondo; Concetta La Rosa - Casa di Cura Villa Verde snc – Taranto. **Sardegna:** Luigi Sannia - ASL Sassari – Sassari. **Sicilia:** Paolo Barbanto - Presidio Ospedaliero M. Ascoli - S. Tommaselli, Azienda Ospedaliera –Catania; Antonio Castello - Ospedale Buccheri La Ferla Fatebenefratelli – Palermo; Rosario Coco - Azienda Ospedaliera Cannizzaro - Dipartimento Cardiovascolare – Catania; Renato Rametta - Azienda Ospedaliera 'San Giovanni di Dio' – Agrigento; Daniele Albanese - Unità di Valutazione Funzionale e Riabilitazione del Cardiopatico, Ospedale Civico A.R.N.A.S. – Palermo; Antonio Circo - Casa di Cura Carmide Villa l'Ulivo – Catania; Rosaria Raciti - Centro Cuore Morgagni – Pedara; Luigi Scarnato - Casa di Cura Regina Pacis - San Cataldo; Flavia Dispensa - Fondazione Istituto San Raffaele Giglio – Cefalù; Leondardo La Spina - Centro Ionico di Cardiologia – Riposto; Alfio Stuto - Star For Life c/o Poliambulatorio di Cardiologia Dr Armario Biagio s.a.s. – Siracusa; Calogero Vasco - Azienda Ospedaliera Umberto I – Enna; Salvatore Gibiino - Diagnostica Cardiovascolare del Dr S. Gibiino & C. snc. – Catania; Michele Gabriele - Ospedale di Mazara Del Vallo - Mazara Del Vallo; Claudio Dispensieri – Azienda Ospedaliera Piemonte – Messina; Vittorio Carini - Casa di Cura Riabilitativa 'Villa Sofia' – Acireale. **Toscana:** Michele Provvidenza - ASL 12 Versilia - Presidio Ospedaliero di Viareggio - Lido di Camaiore; Alessandro Scalzini - ASL 6 Livorno - Presidio Ospedaliero di Cecina – Cecina; Carlo Giustarini - Auxilium Vitae Volterra S.p.A. – Volterra; Claudio Macchi - Fondazione Don Gnocchi Onlus, IRCCS – Impruneta; Francesco Fattiroli - Azienda Ospedaliero Universitaria Careggi – Firenze; Mauro Vannucci - IFCA Villa Ulivella e Glicini – Firenze; Luciana Iacopetti - ASL 3 Pistoia - Presidio Ospedaliero Pescia – Pescia; Mario Cordoni - ASL 6 Livorno - Presidio Ospedaliero di Piombino – Piombino. **Trentino e Alto Adige:** Ferrario Gabriele - Casa di Cura Eremo – Arco; Renato Santoni - Ospedale Classificato San Pancrazio – Arco; Walter Pitscheider - Centro di Riabilitazione del Cardiopatico - Salus Center – Bolzano; Roberto Bettini - Ospedale di Trento – Mezzolombardo; Daniela Girardini - S. Maria del Carmine - Rovereto - Centro di Riabilitazione Cardiologica Ospedale di Ala – Ala. **Umbria:** Sara Mandorla - ASL 1 - Gualdo Tadino – Gualdo Tadino; Fabrizio Anniboletti – ASL 2 Servizio di Cardiologia Ex Ospedale Grocco Perugia – Perugia; Federico Patriarchi - UO Cardiologia Ospedale di Foligno - Nocera Umbra. **Veneto:** Giuseppe Favretto - Ospedale Riabilitativo di Alta Specializzazione S.p.A. - Motta di Livenza; Pier Luigi Baroni - Casa di Cura Villa Garda – Garda; Fede Bordin - ASL N. 4 - Presidio Ospedaliero di Thiene – Thiene; Pietro Biondi - ULSS 8 – Montebelluna; Fabio Bellotto - Istituto Riabilitativo - Cortina D'Ampezzo; Albino Zanocco - Azienda Ospedaliera – Mirano; Andrea Ponchia - ULSS 16 – Padova; Enzo Mantovani - Azienda

ULSS 15 – Camposampiero; Ennio Li Greci - Ospedale Don L. Chiarenzi - AALSS 21 Legnago (Verona) – Zevio; Roberto Carlon - Azienda ALSS 15 Presidio Ospedaliero di Cittadella – Cittadella; Leopoldo Celegon - UO di Cardiologia - Riabilitazione Cardiologica - Castelfranco Veneto; Stefano Baracchi - Ospedale al Mare Lido di Venezia - Lido di Venezia; Grazia Pizzolato - AUSSL N. 10 - San Donà di Piave; Lorenzo Peroni - Policlinico San Marco – Mestre; Enzo Apolloni - Ospedale di Asiago – Asiago; Gianmarco Mosele - Casa di Cura Privata Villa Margherita S.r.l. – Arcugnano; Mario Guarnerio - Ospedale di Feltre – Feltre; Loris Roncon - Ospedale di Rovigo – Rovigo.

## References

- Levy D, Kenchaiah S, Larson MG, *et al.* Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347**:1397–1402.
- Curtis LH, Whellan DJ, Hammill BG, *et al.* Incidence and prevalence of heart failure in elderly persons, 1994–2003. *Arch Intern Med* 2008; **168**:418–424.
- Ferrucci L, Giallauria F, Guralnik JM. Epidemiology of aging. *Radiol Clin North Am* 2008; **46**:643–652.
- Galbreath AD, Krasuski RA, Smith B, *et al.* Long-term healthcare and cost outcomes of disease management in a large, randomized, community-based population with heart failure. *Circulation* 2004; **110**:3518–3526.
- Belardinelli R, Georgiou D, Cianci G, *et al.* Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; **99**:1173–1182.
- Coats AJ, Adamopoulos S, Radaelli A, *et al.* Controlled trial of physical training in chronic heart failure. Exercise performance, hemodynamics, ventilation, and autonomic function. *Circulation* 1992; **85**:2119–2131.
- McKelvie RS. Exercise training in patients with heart failure: clinical outcomes, safety, and indications. *Heart Fail Rev* 2008; **13**:3–11.
- Flynn KE, Piña IL, Whellan DJ, *et al.* Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009; **301**:1451–1459.
- Piepoli MF, Davos C, Francis DP, *et al.* Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328**:189.
- Smart N, Marwick TH. Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity. *Am J Med* 2004; **116**:693–706.
- Griffo R, Urbinati S, Giannuzzi P, *et al.* Linee guida nazionali su cardiologia riabilitativa e prevenzione secondaria delle malattie cardiovascolari: sommario esecutivo. *G Ital Cardiol* 2008; **9**:286–297.
- Worcester MU, Murphy BM, Mee VK, *et al.* Cardiac rehabilitation programmes: predictors of nonattendance and drop-out. *Eur J Cardiovasc Prev Rehabil* 2004; **11**:328–335.
- Giannuzzi P, Temporelli PL, Marchioli R, *et al.* Global secondary prevention strategies to limit event recurrence after myocardial infarction. *Arch Intern Med* 2008; **168**:2194–2204.
- Giallauria F, Vigorito C, Tramarin R, *et al.* Cardiac rehabilitation in very old patients: data from the Italian Survey on Cardiac Rehabilitation – 2008 (ISYDE-2008) - Official report of the Italian Association for Cardiovascular Prevention, Rehabilitation and Epidemiology (GICR-IACPR). *J Gerontol Ser A-Biol Sci Med Sci* 2010; **65A**:1353–1361.
- Piepoli MF, Corrà U, Benzer W, *et al.* Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2010; **17**:1–17.
- Piepoli MF, Conraads V, Corrà U, *et al.* Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011; **13**:347–357.
- Tramarin R, De Feo S, Ambrosetti M, *et al.* The Italian survey on cardiac rehabilitation: a snapshot of current cardiac rehabilitation programmes and providers in Italy. *Monaldi Arch Chest Dis* 2007; **68**:193–198.
- Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**:189–198.
- Cacciatore F, Abete P, Mazzella F, *et al.* Frailty predicts long-term mortality in elderly subjects with chronic heart failure. *Eur J Clin Invest* 2005; **35**:723–730.
- Metra M, Zacà V, Parati G, *et al.* Cardiovascular and non cardiovascular comorbidities in patients with chronic heart failure. *J Cardiovasc Med (Hagerstown)* 2011; **12**:76–84.
- Hawkins NM, Wang D, Petrie MC, *et al.* Baseline characteristics and outcomes of patients with heart failure receiving bronchodilators in the CHARM programme. *Eur J Heart Fail* 2010; **12**:557–565.
- Perego GB, Marenzi GC, Guazzi M, *et al.* Contribution of PO<sub>2</sub>, P<sub>50</sub>, and Hb to changes in arteriovenous O<sub>2</sub> content during exercise in heart failure. *J Appl Physiol* 1996; **80**:623–631.
- Kjaergaard J, Akkan D, Iversen KK, *et al.* Right ventricular dysfunction as an independent predictor of short- and long-term mortality in patients with heart failure. *Eur J Heart Fail* 2007; **9**:610–616.
- Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; **107**:1514–1519.
- He J, Ogden LG, Bazzano LA, *et al.* Risk factors for congestive heart failure in US men and women. NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001; **161**:996–1002.
- Braunstein JB, Anderson GF, Gerstenblith G, *et al.* Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 2003; **42**:1226–1233.
- Giles TD, Sander GE. Diabetes mellitus and heart failure: basic mechanisms, clinical features, and therapeutic considerations. *Cardiol Clin* 2004; **22**:553–568.
- Shlipak MG, Massie BM. The clinical challenge of cardiorenal syndrome. *Circulation* 2004; **110**:1514–1517.
- Felker GM. Diuretic management in heart failure. *Congest Heart Fail* 2010; **16** (Suppl 1):S68–72.
- Vogels RL, Scheltens P, Schroeder-Tanka JM, *et al.* Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007; **9**:440–449.
- Trojano L, Antonelli I, Acanfora D, *et al.* Cognitive impairment: a key feature of congestive heart failure in the elderly. *J Neurol* 2003; **250**:1456–1463.
- O'Connor CM, Abraham WT, Albert NM, *et al.* Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). *Am Heart J* 2008; **156**:662–673.
- Smart NA, Dieberg G, Giallauria F. Intermittent versus continuous exercise training in chronic heart failure: A meta-analysis. *Int J Cardiol* 2011. [Epub ahead of print] doi:10.1016/j.ijcard.2011.10.075
- Smart NA, Dieberg G, Giallauria F. Functional electrical stimulation for chronic heart failure: a meta-analysis. *Int J Cardiol* 2012. [Epub ahead of print] doi:10.1016/j.ijcard.2011.12.019
- Smart NA, Giallauria F, Dieberg G. Efficacy of inspiratory muscle training in chronic heart failure patients: A systematic review and meta-analysis. *Int J Cardiol* 2012 May 3. [Epub ahead of print] doi:10.1016/j.ijcard.2012.04.029