Role of a multidisciplinary program in improving outcomes in cognitively impaired heart failure older patients

Efficacia di un programma multidisciplinare in pazienti con scompenso cardiaco e deficit cognitivo

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BACKGROUND: Despite the availability of effective treatments, management of older heart failure (HF) patients remains sub-optimal with frequent hospital admissions, disability and high mortality rates [1-3]. Older patients include a heterogeneous population in which the clinical status and subsequent risk profile result from a complex interaction between different domains: age-related cardiovascular changes, cardiovascular disease, co-morbidities (not only hypertension, diabetes, renal failure, chronic obstructive pulmonary disease and anemia, but also cognitive impairment, arthritis, incontinence, psychological problems, limitations in activities of daily living and social issues [4, 5].

METHODS: Consecutive (n=173) community-living outpatients aged >70 years (mean 77±6, 48% women) were enrolled in stable clinical conditions. Cognitive status was assessed by means of Folstein Mini Mental State Examination (MMSE).

RESULTS: CI (MMSE<24) was present in 41.6% (42.5% UC vs 40.7% MP p=ns). The variables independently associated to CI were: older age, education level <5 years, anemia and severe renal dysfunction. During a 2-year follow-up, 59 patients died (31.4%) with no significant difference between intervention groups. At multivariate analysis, CI was independently associated to death (HR 2,077[95%CI 1.097-3,931]), HF admissions (2,133[1,346-3,381]), death/HF admissions (1,784[1,132-2,811]) and all-cause admissions (1,473[1,008-2,153]). When considered according to intervention groups, CI was independently associated to all-cause death (3,603 [1,553-8,358], death/HF admissions (2,029[1,200-3,432]) and HF admissions (2,474[1,406-3,533]) but not to all-cause admissions. The assignment of patients with CI to MP was associated to a significant reduction in HF admissions vs UC (0,503[0,253-0,999] (all interaction tests p=ns).

CONCLUSIONS: This study suggests that CI is very common and associated to worse prognosis in heart failure and that hospital-based MP seems to improve outcomes in these patients through reduction of heart failure hospital admission.

Keywords: heart failure, disease management, cognitive impairment, elderly, prognosis.

Cognitive impairment frequently complicates heart failure with deficits being most prominent in the domains of executive function, memory, attention, language, and mental speed and is associated with disability, morbidity and mortality [11-13]. Even mild forms of cognitive impairment may seriously interfere with HF management and self-care through impaired quality of life, decision-making and ability to adhere to complex medication and dietary regimens [14]. In order to improve outcomes in these patients, an approach to enhance adherence to care plan and specific behaviours should be considered. Previous studies reported that nurse-led home-based multidisciplinary program (MP) may not improve the prognosis of this high-risk group [15]. In this sub-analysis of a previously published randomized study comparing MP and usual care (UC) [15], we investigated: 1) the influence of cognitive impairment on outcome of older HF patient and, 2) if a MP represents an appropriate model of care in these patients.

**Methods**

**Study design:** The study was conducted at two hospital HF clinics and primary care facilities. We evaluated consecutive HF patients aged 70 years or more, both males and females, with reduced and normal left ventricular Ejection Fraction and discharged home after a hospitalization due to New York Heart Association (NYHA) functional class III/IV HF, requiring intravenous diuretic and/or inotropes or vasodilators therapy [16]. The diagnosis was determined according to the European Society of Cardiology guidelines [17]. Patients were excluded if they had: 1) valvular heart disease requiring planned surgery, 2) active substance abuse, severe gait impairment, severe dementia and/or MMSE<11 or psychiatric disease, 3) coexisting non-cardiac illness likely to reduce life expectancy, 4) need for long-term intravenous inotrope therapy, 5) unwillingness to provide informed consent, and 6) living in a nursing home or outside the area served by the clinical sites. The protocol is consistent with the Principles of the Declaration of Helsinki and all participants gave their informed consent. No Institutional Review Board approval for this type of study (a non pharmacological trial) was required for at the time of study in our Institution. Details on randomisation and blinding procedures and on the MP intervention have been previously reported [16] (Figure 1). The MP combined outpatient hospital-based and primary care. In each of the two participating teams, the members were a cardiologist, specialized nurses and primary care physicians. The components of the MP were: discharge planning, patient and caregiver education, therapy optimization, improved communication and early attention to signs and symptoms. Intensive follow-up was based on scheduled and unplanned hospital visits, nurse’s phone call and office and home primary care physician visits. Patients assigned to UC received all treatments and services ordered by their primary care physician and/or cardiologist or internist. The follow-up was based on phone calls (to the patient and/or family members or primary care physician) after one, three months from hospital discharge, and thereafter every six months.

**Clinical evaluation and definitions.** Initial assessment included history, physical examination, NYHA class, 12-lead electrocardiogram, Doppler-echocardiography and a multidimensional assessment performed using previously validated instruments that explored the following areas: 1) Socio-economic: years of education, marital status, living arrangement and financial income; 2) ability to perform basic (BADL) and instrumental (IADL) activities of daily living, using two modified 7-item scales [18, 19]; 3) cognitive function, measured with Folstein’s Mini Mental State Examination (MMSE) (with items measuring orientation, registration, attention and calculation, recall, language and visual spatial ability), [20]; 4) depressive symptoms, measured with the 15-item Geriatric Depression Scale (GDS) [21]; 5) Charlson Comorbidity index [22]. Cognitive impairment was defined by a Mini Mental State Examination score less or equal than 24. Physical disability was defined as need of assistance in performing at least one basic or two instrumental Activities of Daily Living.

**Outcome measures.** Planned outcome variables were all-cause deaths, all-cause and HF-related admissions the composite of death from any cause and/or hospital admissions for HF and total costs of care. All patients were followed for two years and clinical status, medications, number of primary care and specialist visits and events were recorded at each visit or phone call. Events were collected also using phone calls, discharge reports, hospital and administrative databases, death certificates and were blindly evaluated by a central endpoint committee composed of three cardiologists, who had no knowledge of the randomization group assignment. All questionnaires were analyzed by researchers blinded to intervention group assignment.

**Estimation of costs.** In this study the National Health System (NHS) perspective was adopted, as in Italy it provides all health care services for patients affected by moderate-to-severe HF. Data on resource utilization of MP compared to UC have been previously published [16]. Costs were collected prospectively and only comprised direct costs (pre-discharge education and assessment, medications, hospital and home visits, echocardiography and hospitalizations) calculated on the basis of NHS charges at the time of the study and stratified according to the presence or absence of cognitive impairment.

**Statistical analysis.** Groups were compared by the t test for normally distributed continuous variables and expressed as means ± standard deviations (SDs), the chi square test and Fisher exact test for
categorical variables (expressed as counts and percentages). Logistic regression analysis was performed in order to identify factors potentially related to cognitive impairment (MMSE score < 24) with calculation of adjusted odds ratios (OR) and 95% confidence intervals (CIs). Outcome analysis was conducted according to an intention-to-treat approach. Multivariable Cox proportional-hazards models with adjustment for potentially confounding variables were used to estimate the risk of outcomes. Differences in treatment effects according to cognitive groups were evaluated by tests of interaction and the statistical significance was determined by a Wald chi-square test for interaction. Four Kaplan-Meier stratified survival curves were then generated to compare – using Mantel-Cox log rank test – the event-free survival of patients with and without cognitive impairment in the usual care group and MP group. Data for all event-free patients were censored on study day 730. A p value less than 0.05 was considered significant. Analyses were performed using SPSS for Windows 13.01 (SPSS Inc. USA).

Results

During a two-year period, 173 patients (mean age 77±5, range 70-94; males 52%) from a consecutive cohort of 236 (78% inclusion rate), were randomized to MP (n=86) or UC (n=87) (Figure 1). Mean left ventricular ejection fraction (LVEF) was 33.4±10.7 and mean NYHA class was 2.7±0.6 (60.7% NYHA 3-4). Previous MI was present in 92 (53.2%) patients. All patients were treated with optimized evidence-based therapy (Beta-blockers 53.8%, ACE-inhibitors or Angiotensin Receptor Blockers 91.9%, Spironolactone 35.1%).

Clinical correlates of Cognitive impairment. Cognitive impairment was present in 72 patients (41.6%; 42.5% of usual care patients, 40.7% of MP patients p=ns). Table 1 shows the baseline characteristics of patients according to cognitive function. At multivariate logistic regression analysis the variables independently associated to CI were: age older than 80 years, education level < 5 years, anemia and severe renal dysfunction. (Table 2). No association was found with blood pressure, LVEF or history of atrial fibrillation, hypertension and diabetes.

Outcomes. At two-year follow-up there were 59 deaths, 96 deaths and/or HF admissions, 113 all-cause admissions and 77 HF admissions. As a whole, MP intervention resulted in a significant reduction in deaths and/or HF admissions, and HF admissions [16].

When the entire cohort was analysed, cognitive impairment was independently associated to higher incidence of events (Table 3, unadjusted chi-square test p values). At multivariate analysis, the risk of all-cause death increased more than 2-fold (HR 2.077[95%CI 1.097-3.931]) in patients with cognitive impairment; other independent predictors of mortality were: age, left ventricular ejection fraction<20%, hypotension, anemia, disability, and absence of Beta-blocker therapy (Table 4). Cognitive impairment was also independently associated to more frequent HF admissions (2.133[1.346-3.811]), more frequent death and/or HF admissions (1.784[1.132-2.811]) and all-cause admissions (1.473[1.008-2.153] (Table 4).

Differences in treatment group (MP vs usual care) effects were then stratified and evaluated according to cognitive groups in a multivariate Cox model. Cognitive impairment was equally associated to all-cause death (3,603 [1,553-8,358], death/HF admissions (2,029[1,200-3,432]) and HF admissions (2,474[1,406-4,353]) but not to all-cause admissions. The assignment of patients with cognitive impairment to MP was associated to a significant reduction in HF admissions vs usual care (0.503[0,253-0,999] (all interaction tests p=ns). Figure 2 shows the event-free survival curves for the two treatment groups stratified according to cognitive status and compared by means of Log-rank Mantel-Cox tests. In both treatment groups, those with cognitive impairment appeared to have a worse prognosis, the risk of death and death/HF admission in MP patients being similar to those in usual care. By contrast, for HF admissions, a significant effect of both cognitive function and group assignment was observed, suggesting that the intervention is of benefit also in cognitively impaired patients. The risk of being admitted for HF was similar in patients with cognitive impairment enrolled in the MP and in cognitively intact patients in usual care. For all-cause admissions only a significant effect of group assignment was observed, with cognitively intact patients assigned to MP reporting a significant improvement (Figure 2).
### Tabella 1. Clinical features according to presence or absence of cognitive impairment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with MMSE(&lt; 24) (n 72)</th>
<th>Patients with MMSE(\geq 24) (n 101)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>79,4±5,7</td>
<td>75,3±3,9</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>Older than 80 years</td>
<td>28 (38,9)</td>
<td>14 (13,9)</td>
<td>&lt;0,0001</td>
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<tr>
<td>Men (%)</td>
<td>27 (37,5)</td>
<td>63 (62,4)</td>
<td>0,001</td>
</tr>
<tr>
<td>Body mass Index (Kg/m²)</td>
<td>23,5±4,3</td>
<td>25,1±3,7</td>
<td>0,016</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>75±12</td>
<td>71±14</td>
<td>Ns</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>132±19</td>
<td>131±21</td>
<td>Ns</td>
</tr>
<tr>
<td>NYHA III-IV class</td>
<td>48 (66,7)</td>
<td>57 (56,4)</td>
<td>Ns</td>
</tr>
<tr>
<td>Single marital status</td>
<td>34 (48,6)</td>
<td>32 (32,0)</td>
<td>0,029</td>
</tr>
<tr>
<td>Living alone</td>
<td>12 (16,7)</td>
<td>26 (25,7)</td>
<td>Ns</td>
</tr>
<tr>
<td>Low income level *</td>
<td>16 (22,5)</td>
<td>7 (7,1)</td>
<td>0,004</td>
</tr>
<tr>
<td>Education level &lt; 5 yrs</td>
<td>61 (84,7)</td>
<td>38 (37,6)</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>Heart Failure etiology</td>
<td>Ischemic</td>
<td>40(55,6)</td>
<td>53(52,5)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>5(6,9)</td>
<td>17(16,8)</td>
<td></td>
</tr>
<tr>
<td>Dilated</td>
<td>12(16,7)</td>
<td>11(13,9)</td>
<td></td>
</tr>
<tr>
<td>Valvular</td>
<td>11(15,3)</td>
<td>4(5,6)</td>
<td></td>
</tr>
<tr>
<td>Other/multiple</td>
<td>4(5,6)</td>
<td>5(5)</td>
<td></td>
</tr>
<tr>
<td>CKD ≥IV Stage **</td>
<td>33 (45,8)</td>
<td>14 (13,9)</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>Anemia #</td>
<td>50 (69,4)</td>
<td>48 (47,5)</td>
<td>0,004</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>138±4</td>
<td>138±4</td>
<td>Ns</td>
</tr>
<tr>
<td>Previous Myocardial infarction</td>
<td>35 (48,6)</td>
<td>57 (56,4)</td>
<td>Ns</td>
</tr>
<tr>
<td>Permanent Atrial Fibrillation</td>
<td>22 (30,6)</td>
<td>22 (21,8)</td>
<td>Ns</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>46 (64)</td>
<td>66(65)</td>
<td>ns</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>26(36)</td>
<td>29(29)</td>
<td>Ns</td>
</tr>
<tr>
<td>History of COPD</td>
<td>26 (36,1)</td>
<td>37 (36,6)</td>
<td>Ns</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>2,5±1,8</td>
<td>1,9±1,3</td>
<td>&lt;0,01</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>33,7±11,7</td>
<td>33,1±9,9</td>
<td>ns</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>32 (44,4)</td>
<td>61 (60,4)</td>
<td>0,038</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>59 (81,9)</td>
<td>81 (80,2)</td>
<td>Ns</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers</td>
<td>6 (8,3)</td>
<td>13 (12,9)</td>
<td>Ns</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>28 (38,9)</td>
<td>29 (28,7)</td>
<td>Ns</td>
</tr>
<tr>
<td>MMSE mean score</td>
<td>21±3,6</td>
<td>28±1,6</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>≥1 BADL Disability §</td>
<td>32 (44,4)</td>
<td>13 (28,9)</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>≥2 IADL Disability §</td>
<td>53 (73,6)</td>
<td>29 (28,7)</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>GDS 15 score &lt;6</td>
<td>56 (77,8)</td>
<td>52 (51,5)</td>
<td>&lt;0,0001</td>
</tr>
<tr>
<td>Total direct costs of care</td>
<td>4233,04±3397,00</td>
<td>4744, 92±3380,00</td>
<td>Ns</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease; BADL: Basic activities of daily living; IADL: Instrumental activities if daily living; MMSE: Mini mental state examination; GDS 15: 15-item Geriatric Depression Scale; * defined from the National Statistic Institute as an income <600.00 € and <900.00 € for one person and for a two-person family, respectively; ** defined as an eGFR (glomerular filtration rate) <30 ml/min/m²; # defined as Hemoglobin <12 g/dl; § defined as impairment in at least one BADL or two IADL.
Estimation of direct costs. The mean two-year costs of care were similar in patients with and without cognitive impairment (€4233.04±3397.00 vs €4744.92±3380.00; p=ns) (Table 1). The total cost in the MP group was €3397.00±3397.00 in patients with cognitive impairment and €3034.92±3380.00 in patients without (p=ns). The total cost of care in usual care group was €4386.21±3342.73 in patients with cognitive impairment and €4386.21±3342.73 in patients without (p=ns).
Available evidence [6-8] suggests that HF MPs are a consistent way to provide appropriate, more comprehensive and cost-effective care. In older HF patients many re-admissions can be often attributed to co-morbidities, behavioural and social factors rather than to deteriorating cardiac function or an incident cardiac event. Older patients are also less likely to receive recommended therapies, in part because clinical trials of HF therapy have ignored outcomes of importance to this population, including comorbidities and impaired cognitive function [2, 4, 5]. Cognitive impairment represents a risk factor for low adherence to treatments, disability, hospitalization and death. Nevertheless, it has been rarely assessed in previous studies on HF [11-14], and it is still not well established if reported models of intervention are effective in these patients [6-8, 23].

The results of this perspective study confirm that cognitive impairment is a prevalent condition associated to a worse prognosis, and suggest that a hospital-based, integrated MP may improve outcomes in these patients through reduction in HF hospital admission.

Cognitive impairment is significantly and independently associated to a higher risk of adverse outcomes also in patients in optimised therapy followed by specialists, suggesting that attention for this non-cardiovascular comorbidity seems to be essential for optimizing treatment and improve prognosis. It is of note that cognitive impairment, as well as other variables such disability or frailty are seldom included in statistical models and patient predictors of readmission for HF [24].

Previous published trials on MPs rarely examined the relative effectiveness of the intervention among cognitively impaired patients. In HF patients, cognitive impairment contributes with social and behavioral problems in making difficult to engage in self-care, in decreasing compliance to care-plan and prescribed therapy in a safe and effective manner and, consequently, increasing hospital admissions [14]. Moser et al. pointed out the role of cognition in their conceptual framework of factors affecting decision making and subsequent self-care in patients with HF [25]. Cognitive impairment may contribute to failed self-care in two ways: through deficits in memory and attention that may impair treatment adherence, because of forgetfulness and...
poor learning ability, and through problems in executive functions, information processing and decision making in complex situations, such as early recognition and interpretation of symptoms and seeking care [26]. McLennan et al., reported that a nurse-lead home-based multidisciplinary program may not improve the prognosis of patients with mild cognitive impairment. We observed similar findings with regards to all-cause mortality, but not HF readmissions or the combined end-point. However the model of intervention and the follow-up duration were significantly different than that used in the present study [15]. Our findings clearly demonstrate that enrolment in a MP is associated with a clinically important and sustained decline in HF hospital admissions over a 2-year intervention period in comparison to usual care, also in patients with mild-to-moderate cognitive impairment. The risk of being admitted for HF was similar in patients with CI enrolled in the MP and in cognitively intact patients in usual care (Figure 2). Moreover, economic analysis suggests that MP does not increase direct costs of care also in patients with mild-to-moderate CI.

A possible reason for the favourable effect of a MP on HF admissions is that cognitively impaired patients may need intensive education program and follow-up through office or home visits or telephone contacts to prevent adherence issues, a major cause of re-hospitalization. Written and given verbally care instructions and medication or dietary changes are necessary because of patient difficulties with information requiring attention, learning, and memory functions. Our MP provided clinical monitoring and a structured and continuing education to the patient and their caregiver according to guidelines [17, 27]. Thus, a rapid assessment of cognitive function, particularly in patients of advanced age, with poor social status, anemia or renal dysfunction, may lead to a more intensive follow-up and tailored education in order to reduce the risk of non-adherence, reduced self-care and re-hospitalisation.

Limitations. The strengths of the present study are the accuracy of clinical and instrumental evaluation, the clinical and hemodynamical stability at the time of assessment, the optimisation of evidence-based treatments and the completeness and duration of follow-up. However, it deserves several limitations. First, this study excluded those patients with severe cognitive impairment in which disability, low-compliance and incidence of events in the final stages of the syndrome are extremely high, more likely to follow-up with intensive, home-based programs [6-8, 22, 23]. Thus, it is likely that not all community-dwelling older patients will benefit from such a model of intervention.

Second, cognitive function, disability and quality of life are complex and time-consuming to measure. In our study cognitive evaluation was performed using a limited number of tests instead of an extensive and more accurate but also time-consuming battery. Moreover, the MMSE has poor sensitivity and specificity versus memory dysfunction, and in the detection of very mild forms of cognitive impairment [13, 28]. Thus, a screening instrument for easy use in clinical practice more sensitive than MMSE needs to be identified. However, the tests included in the present study were selected from those available on the basis of recognised reliability [11] as well as usability in a real-world ambulatory setting, where time and personnel resources are of importance. In this view, this study suggest that also a short minimal data set is useful and applicable for screening purposes in a HF clinic.

In conclusion, in spite of optimized therapy and specialist care, CI is very common and associated to worse prognosis in HF and hospital-based, integrated MP appears to be equally effective in mild-to-moderately cognitively impaired patients through reduction in HF hospital admission.

These results – if confirmed – may have clear implications in clinical practice and can be a useful contribution for an optimal allocation of healthcare resources [27]. A multidisciplinary approach is necessary to deal with the complexity of this clinical syndrome and assessment of cognitive function, even by the simple screening tests used in this study, should be part of the baseline evaluation [29, 30].

Contributors. GiP, DDS, ADL, LT and GC were involved in planning the study and wrote the study protocol and the manuscript. GiP and DDS prepared summaries of all hospital admissions for the end point committee (GM, LT, GC). GiP and DDS supervised the activity of the enrolling HF clinics and provided medical support. MDT, ST and LM collected and assembled the clinical data. GB and GiP carried out the statistical analysis. All investigators were involved in reviewing the manuscript.

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<5 anni., anemia e disfunzione renale severa. A 2 anni di follow-up, 59 pazienti sono morti (31.4%) senza differenze significative tra i gruppi. All'analisi multivariata, nell’intera coorte, il deficit cognitivo era associato a morte (HR 2.077[95%CI 1.097-3.931]), ricoveri per SC (2.133[1.346-3.811]), morte/ricoveri per SC (1.784[1.132-2.811]) e ricoveri per tutte le cause (1.473[1.008-2.153]). Stratificando per gruppi di intervento, il deficit cognitivo era ancora associato alla mortalità totale (3.603 [1.553-8.358], morte/ricoveri per SC (2.029[1.200-3.432]), ricoveri per SC (2.474[1.406-4.353]). I pazienti con deficit cognitivo assegnati a MP riportavano una riduzione significativa di ricoveri per SC (0.503[0.253-0.999] (test di interazione p=ns).

**Conclusioni:** Il deficit cognitivo è molto comune e associato a prognosi pessimo nello SC e un programma multidisciplinare sembra migliorare la prognosi in questi pazienti attraverso una riduzione dei ricoveri per SC.

**LIST OF ABBREVIATIONS**

CI: cognitive impairment  
HF: heart failure  
MP: multidisciplinary program  
UC: usual care  
MMSE: Mini Mental State Examination  
HR: hazard ratio  
NYHA: New York Heart Association  
BADL: basic activities of daily living  
IADL: instrumental activities of daily living  
GDS: Geriatric Depression Scale  
NHS: National Health System  
SD: standard deviation  
CI: confidence interval  
LVEF: left ventricular ejection fraction  
MI: myocardial infarction  
eGFR: glomerular filtration rate

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**References**


