A prospective, controlled study of a disease management program for elderly with heart failure.

STUDY PROTOCOL

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INDEX

1.Synopsis

Elderly heart failure patients are at high risk of events. Available studies and systematic reviews suggest that elderly patients benefit from disease management programs (DMP). However, important questions are still open, including the optimal follow-up intensity and duration and whether such interventions are cost-effective during long-term follow-up and in different health care systems. The primary aim of this study is to determine the long-term efficacy of a hybrid disease management program in consecutive older outpatients. Moreover, because elderly represent a heterogeneous population, the secondary aim of this study is to determine which patients benefit mostly from a DMP, by means of their frailty profile. Intervention will consist in combined hospital- (cardiologists and nurse-coordinators from 2 heart failure clinics) and home-based (patient's general practitioner visits) care. The components of the DMP are: discharge planning, education, therapy optimization, improved communication, early attention to signs and symptoms. Intensive follow-up was based on scheduled hospital visits (starting within 14 days of discharge), nurse's phone call and home general practitioner visits. A comprehensive multidimensional assessment will be performed prospectively in all patients at baseline

2. Introduction.

Clinical management of older heart failure patients remains sub-optimal with subsequent high risk of mortality, morbility, poor quality of life and increasing costs, despite the availability of effective treatments (1-4). Available studies and systematic reviews suggest that elderly patients benefit from disease management programs (DMP) designed to improve quality of care and patient compliance and reduce hospital admissions with a beneficial cost-effectiveness ratio (5-10). However, results on other end-points and mortality are inconclusive. Furthermore, important questions are still open, including the most appropriate patient's selection process, the optimal follow-up intensity and duration and finally, whether such interventions are cost-effective during long-term follow-up and in different health care systems (7-10). Elderly patients include a heterogeneous population where the clinical status and subsequent risk profile result from a complex interaction between different domains (8): age-related cardiovascular changes, cardiovascular disease, comorbid conditions, age-related impairments and social issues (9). Multidimensional assessment (MA) is a validated diagnostic process to determine the medical, psychological, and functional capabilities and aimed at providing information for appropriate choice of care-plan and follow-up. One of the major goals of the MA is the identification of frailty. Frailty is a clinically recognized syndrome of loss of reserves (energy, physical ability, mobility, cognition, health) that gives rise to an increased vulnerability to stressors (e.g., concomitant acute illnesses, hospitalizations, medical procedures) and the risk of major events such as low-compliance, falls, disability, hospitalization and death, in subjects with or without HF. Although the focus of MA is the frail or disabled elderly , this approach was rarely used in previous studies on HF and never used to evaluate model effectiveness.

3. Aims of the Study

The primary aim of this study is to determine the long-term efficacy of an interdisciplinary DMP involving cardiologist, primary care physician and nurse, combining pre- and post-discharge care and following patients for two years. The secondary aim is to evaluate if the frailty profile should be useful to identify which HF elderly patient may benefit mostly from a DMP and select the appropriate model of care.

4. Study plan, Patients and methods

Objectives. The study is designed as a randomized open trial conducted at two hospital heart failure clinics, comparing a DMP and usual care (UC). The primary end-point of the study is the composite of death from any cause and hospital admissions for heart failure. Other planned outcome variables are all-cause and heart failure hospitalizations, the cumulative number of hospitalizations, all-cause and heart failure related mortality, quality of life, perceived health status, functional status and indexes of quality of care, such as the percentage of patients receiving beta-blockers.

Eligibility of patients.

Inclusion criteria are as follows: age 70 years or more and discharged home after a hospitalisation due to heart failure, defined as an admission in New York Heart Association (NYHA) functional class III/IV of at least 24 hours requiring specific intravenous diuretic and/or inotropes or vasodilator therapy. The diagnosis will be determined according to the European Society of Cardiology guidelines (11).

Patients will be excluded if they have: 1) valvular heart disease requiring planned surgical correction, 2) active substance abuse, severe gait impairment or confined to bed, severe dementia or psychiatric disease likely to limit compliance, 3) concurrent noncardiac illness likely to reduce life expectancy , 4) need for long-term intravenous inotropic therapy, 6) unwillingness to provide informed consent, 7) living in a nursing home or outside the area served by the clinical sites.

Eligible patients will be randomised and informed consent will be given on the basis of information relevant to the allocated study group. This procedure will avoid bias arising from UC patients being informed of the intervention strategy. It is presumed that this information is likely to influence outcome as some controls would employ the intervention strategy on their own initiative.

Measurments.

In both groups initial assessment will include history, physical examination and a multidimensional assessment (12) including education, marital status, financial income, social and emotional support, ability to perform basic (BADL) and instrumental (IADL) activities of daily living (13,14), cognitive status measure by means of the Folstein Mini Mental Status Examination, depressive symptoms measured by means of the Geriatric Depression scale, comorbidity will be quantified with the Charlson Comorbidity index (15), quality of life and self-perceived health, evaluated, respectively with the Minnesota Living with Heart Failure (MLwHF), a 5-item scale (from very good to very poor) and the EuroQOL (16). Disability is defined as an impairment in at least two IADL or at least one BADL.

An ad-hoc translated and validated local version of the European Self Care Behaviour scale (ESCB) will be administered in order to evaluate the baseline level of self-care (17). Frailty is measured by means of a modified frailty score (FS) (22), calculated combining five domains of functioning (age over 80, cognitive impairment defined as a MMSE score $\leq$24, reduced mobility, urinary incontinence and physical impairment defined as a NYHA functional class III-IV) into six stages of increasing impairment. Stage 1 included patients <80 years, in II NYHA class and without impairments in mobility, continence, or cognitive function. Stages 2 to 6 included patients with the presence of one, two, three, four or all of the specific items, respectively. The risk profile of each patient will be also calculated by means of a prognostic score index .

Intervention

All patients will be discharged on optimized therapy and will receive before randomization a detailed summary and a standardized educational program focused on low-salt diet and drug therapy, self monitoring of blood pressure and symptoms, daily weight, smoke cessation, fluid intake and daily physical activity.

DMP Group. The program is based on a hybrid model, combining hospital clinic- and home-based care. In each of the two participating teams, the members will be a cardiologist experienced in geriatrics, two-to-four specialized nurses and the patient's primary care physician. According to ESC guidelines, the components of the program are: discharge planning, continuing education, therapy optimization, improved communication with health care providers, early attention to signs and symptoms and flexible diuretic regimen (11).

A written list of recommendations, a weight chart, a contact number available 6 hours/day and an educational booklet will be provided only to these patients. They will be encouraged to present their discharge/visit summary and weight chart at all visits. Follow-up is based on hospital clinic visits, periodical nurse's phone calls and home or office primary physician visits.

The cardiologists are the case managers, designed and documented the treatment plan. Hospital visits will occur in the heart failure clinics within 7 to 14 days from discharge and, therefore at 1, 3 and subsequently each 6 months. At each visits patients will receive reinforcement of education and optimization of therapy. Nurses will made follow-up phone calls to patients, receive the patient's calls and contacted patients when they did not present to scheduled visits. They could not modify therapy, however, they could recommend that the patient consults the cardiologist or primary care physician when the patient's status deteriorated abruptly or the patient experienced a significant problem

requiring prompt attention. The nurses also play a pivotal role in education program and coordination of patient's management. The primary care physicians are asked to assess adherence to treatment, evaluate possible adverse drug reactions and identify and possibly treat at home signs of worsening clinical condition, concurrent infections or comorbidities and potential precipitating factors, as well as dietary regimen. They will manage all problems not related to heart failure, receive regular written updates from the hospital team and will be notified of abnormal laboratory and clinical values.

Usual care. After discharge, patients assigned to UC will receive all treatments and services ordered by their primary care physician and/or personal cardiologist. The baseline clinical evaluation and therapeutic plan are documented in the patient's chart. In this group vital status and events are recorded by means of phone calls performed every six months.

Outcomes. Patients will be followed for at least two years and outcome data will be obtained at every visit. All in- and outpatient activities are monitored through medical records and contacts with primary care physicians. 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, hospital and administrative databases . Outcomes are evaluated in a blinded manner by a central endpoint committee composed of three cardiologists, who have no knowledge of the treatment assignment. Two members will independently evaluate all cases. In the event of a discrepant classification, the third member reviews the report and assigns the final classification. All MA questionnaires will be analyzed in a blinded fashion.

Estimation of costs. In this study the National Health System (NHS) perspective will be adopted, as in Italy it provides all health care services for patients affected by moderate-to-severe HF. Data on resource utilization will be collected prospectively and will only comprise direct costs (pre-discharge education, medications, management program and usual care and hospitalizations) calculated on the basis of NHS charges at the time of the study and stratified according to the level of frailty. The costs of the hospital-based outpatient program are derived on the basis of the total of telephone calls (mean 15 minutes each) and visits (mean 30 minutes each). The average cost for one HF hospitalization, according to standard mean tariff for Diagnosis-Related Group (DRG) 127 at the time of the study is € 3184.26. For non-HF related admissions, individual DRG tariffs will also be calculated. The initial admission is not included in the cost analysis.

The costs of daily medical therapy (digitalis glycosides, diuretics, beta-blockers, calcium channel blockers, other vasodilators, anti-arrhythmic drugs, ACE inhibitors, angiotensin receptor blockers and anticoagulants), will be estimated using the average dose of therapy to calculate the number of tablets

taken during the follow-up and multiplying this number by the cost per tablet reported in the annual National Therapeutic Formulary. These costs will be actualized by assuming an annual rate of increase of 5%. Indirect costs are difficult to evaluate and will not be considered.

Economic analysis. Economic analysis is based on cost-effectiveness analysis (CEA), in which the alternative interventions are examined in the light of total cost per unit of health outcome. Incremental cost-effectiveness ratios will be calculated for the different frailty profiles, as the cost incurred to prevent one event, given that there was a significant reduction in the primary and secondary end-point, all-cause- and HF-related admissions, non-HF related admissions between groups. The time horizon will be equivalent to that observed during the period of the study (ie, no future projections are made). Moreover, a cost-utility analysis is programmed, calculating quality-adjusted life years (QALY) for each intervention group using the survival method and EuroQOL index as utility. To examine the impact of change in one or more variables on the results of the analysis, a sensitivity analysis where the cost of DMP and hospitalizations are changed of ± 10% will be performed.

Study sample.

Based on previous studies (5,6), metanalyses (7-10) and national databases (3), the study sample is calculated to detect at least a 40% relative reduction at two years in the outcome of death and/or unplanned readmission for heart failure in the DMP, based on the assumption of a 60% event rate for the control group with a 0,05 alpha and 0,90 power. The planned sample size is at least 92 patients per group or, alternatively, the occurrence of 88 events.

Statistical Analysis.

In the primary Study, the two groups will be compared by the *t* test for normally distributed continuous variables and the chi square test for nominal variables (with calculation of odds ratio [OR] and 95% confidence intervals [CI] where appropriate) and the Fisher exact test for variables with a prevalence <5%. Analyses are conducted according to an intention-to-treat approach. Kaplan-Meier survival curves are constructed to assess differences in deaths or readmissions between groups and compared using the log rank test. Data for all event-free patients are censored on study day 730. Event-free survivals are tested with the Cox proportional hazards method. Logistic regression analysis will be performed in order to identify factor potentially related to non-adherence to the program.

In the Secondary Study: Groups will be compared by the t test for normally distributed continuous variables (with Bonferroni correction as appropriate) and the chi square test and Fisher exact test for

nominal variables. The predictive value of the Frailty Score and prognostic score index for the primary end-point will be compared by means of receiver operating curves (ROC). The intervention groups and frailty subgroups will be compared using multiple Cox proportional-hazards models, without and with adjustment for potentially confounding variables: age, sex, NYHA III-IV class, ischemic etiology, diabetes mellitus, atrial fibrillation, systolic blood pressure <100 mmHg, ejection fraction, anemia (hemoglobin ≤12 g/dl), serum sodium and creatinine levels, beta-blocker and ACE-inhibitor or Angiotensin receptor blockers treatment. NYHA III-IV class was not included in multivariable analysis of patients in stage 1 and stages 4-6. Differences in treatment effects according to frailty subgroups will be evaluated by tests of interaction and the statistical significance determined by a Wald chi-square test for interaction. Effects will be omitted from tables when a too small number of events were observed in the given analysis.

All analyses will be performed using SPSS for Windows (SPSS Inc. USA).

5. Variables collected

1. **Baseline Demographic Characteristics and Multidimensional assessment**.

Age (years)
Gender (% Males)
Education (years)
Single/widowed/divorced (%)
Living alone (%)
Low financial income*
No social/family support
≥2 IADL dependency**
≥1 BADL dependency**
MMSE score
Mean GDS 15 score

2. **Baseline Clinical Characteristics**

Body Mass Index (Kg/m^2)
Systolic Blood pressure (mmHG)
Heart rate (b/min)
Heart Failure etiology (Ischemic, Hypertensive, Dilated, Valvular, Other/multiple)

Charlson comorbidity index §
Comorbidities (Hypertension, Diabetes mellitus, Previous myocardial infarction, COPD
NYHA class at discharge
Mean LVEF (%)
Serum Sodium (mmol/l)
Creatinine clearance (ml/min)
Hemoglobin (g/dl)
Treatments at discharge: ACE-inhibitors, Angiotensin receptor blocker, Beta-blockers, Mean daily furosemide dose (mg), Spironolactone, Digoxin, Amiodarone, Nitrates, Anticoagulants

3. **Outcomes.**

   Primary outcome variable: death from any cause and/or hospital admissions for HF.
   Secondary end-points: total and cardiovascular mortality, all-cause and HF-related admissions
   Costs of care

4. **Quality of life and functional status.**

Modified Frailty Score: Stage 1-6
EuroQol Index
Mean ESCBs score

5. **Quality of care.**

Clinical status (NYHA)
Number of primary care and specialist visits,
Electrocardiograms and echocardiograms,
Number of telephone calls, number of home primary care visits,
Medications,ACE-inhibitors and Beta-blockers at follow-up

6. **Estimate of costs.**

Pre-discharge Education

Medications
Echocardiography
Cardiology visits
Telephone support
Primary Care office visits
Primary Care home visits
Total outpatient cost, Mean outpatient cost (Standard deviation)
HF admissions, Non HF admissions, All-cause admissions
Total inpatient cost, Mean inpatient cost (Standard deviation)
Total costs, Mean total costs , (Standard deviation)
Mean saving per patient (delta DMP-UC total costs)

7. Economic analysis

CEA (ICER)
QUALY

Ethical issues

The protocol is consistent with the principles of the Declaration of Helsinki and all participants will gave their written informed consent. No Institutional Review Board review for this type of study (non pharmacological trial) is required for at the time of study in our Institution.

Coordination of the Study

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Appendix: study plan