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Design and assessment of disease management program for cardiac patients via enhanced telemedicine with data-mining and pattern recognition

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La conoscenza

è orgogliosa

per aver

imparato tanto,

la saggezza

è umile

per non saperne

abbastanza

(William Cooper)

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Paolo

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1. Introduction

Cardiovascular diseases and in particular Chronic Heart Failure (CHF) represent one of the challenge to be faced by National Health System, because of their mortality and morbidity[2], related expenditure[3] and huge impact on health-related quality of life[4]. Limited health funding and rapidly expanding population of older patients with CHF are leading many National Health Services (NHSs) to search for new programs of care, which allows providing high-quality care in settings alternative to hospitals ones. Home-monitoring (HM) and Disease Management Programs (DMP) were widely explored in the last years because, compared to usual care, they can provide specialised care to a larger number of patients with a limited access to healthcare services. Moreover, both HM and DMP are effective alternatives to UC for management of CHF, reducing mortality and readmission rate[5]. A wide literature investigates their effects on clinical outcomes of patients suffering from CHF[5-14]. In almost the totality of study, those models have been compared to UC, and there is not sufficient literature comparing directly HM and DMP[15-17]. This comparison is needed since some National Health Services (NHSs), as the Italian one[18], are promoting the adoption of HM as an alternatives to UC, while preliminary studies proved that, although HM could be slightly more effective than DMP, HM is up to five times more costly than DMP[19], and therefore less cost-effective. Therefore, the first aim of the current thesis is to provide a systematic comparison of efficacy of HM benchmarked with DMP, which is reported in the chapter 1. Moreover, I contribute to the project and design of a telemedicine service enhanced with data-mining and pattern recognition. In the chapter 2, the design of the telemedicine platform is described and the details about the data-mining application for Heart Failure detection and assessment are reported. In the chapter 3, the results relative to a data-warehouse for hypertensive patients is reported.

Finally, the chapter 4 presents the results of the research for prediction of long-term survival in the elderly.

2. Model of care for Chronic Cardiac Patients

2.1 Disease Management Programs

Nowadays, Disease Management Programs (DMP) are considered valid alternatives to usual care for management of Chronic Heart Failure, reducing mortality and readmission rate[5].

DMP[9, 21] are models of care which consist in coordinated and multidisciplinary healthcare interventions and communications for populations with conditions in which patient self-care efforts are significant. DMP are mainly oriented to five chronic diseases: ischemic heart disease, diabetess, COPD, asthma and heart failure. DMP generally include telephone calls, during which patients interact with trained nursing professionals, and require an extended series of interactions, including a strong educational regarding lifestyle. Patients and their relative are expected to play an active role in managing their diseases[22].

From a literature research (for details about the keywords adopted see section 2.3), 31 randomized clinical trials (RCTs) comparing DMP and usual care in patients suffering from CHF were identified. The most important information of these studies were reported in the Table 1

Table 1: characteristics of the studies comparing Disease Management Programs with Usual Care

Atienza F, 2004	
Participants	338 patients admitted with decompensated Heart Failure
Mean age	68 (median)
Male percentage	60%
Country	Spain
Interventions	On admission, all patients with heart failure considered for inclusion were managed by the responsible cardiologist according to guidelines published at the time of designing the study. The intervention program consisted of three phases. In the first phase, the patients and their families received formal education about the disease. Prior to discharge, the research cardiac nurse had an in-depth interview with the patient and caregivers.

Specifically, the nurse assessed the patient knowledge of the disease, the ability to identify signs and symptoms of heart failure worsening, and the most common responses to the situations of deterioration. This education session included explanations of symptoms and signs of heart failure decompensation, importance of self-monitoring of vital signs, diet and exercise counselling, effects of medications and importance of compliance, and measures to be taken in case of worsening. Individualized strategies were used to improve treatment adherence and to empower patients to manage health problems (i.e. diuretic self-adjustment). All this process was supported by using a teaching brochure developed by the study investigators. The patient was discharged home by the responsible cardiologist who prescribed treatment without knowledge of the assignment group.

In the second phase, a visit with the primary care physician was scheduled within 2 weeks of discharge. The aims of this visit were to monitor patients' clinical progress, identify incipient physical signs of decompensation, and reinforce the educational knowledge. When the patient showed clinical signs of worsening, the primary care physician was allowed either to modify the discharge treatment or to refer the patient to the hospital for reassessment.

During the third phase, regular follow-up visits at the outpatient Heart Failure Clinic were scheduled every 3 months where, in addition to the routine clinical assessment, the cardiologist reviewed the patients' performance and introduced correcting strategies to improve treatment adherence and response. This visit reinforced patients' knowledge of the illness and increased their ability to manage health problems. The heart failure specialist coordinated visits to other specialists, diagnostic tests and treatments prescribed by other instances. The telemonitoring phase lasted from discharge until the end of the study and consisted of a facilitated telephone communication with a monitor (SCT), providing a 24-h mobile phone contact number. The heart failure clinic team was also available for consultation during working hours. Patients were instructed to contact the monitor or the heart failure team in case of doubts or signs of worsening.

Control group patients received discharge planning according to the routine protocol of the study hospitals. To avoid

Atienza F, 2004

	contamination of the control group management, additional follow-up was performed by primary care physicians and cardiologists not participating in the study.
Outcomes	Readmission, mortality, quality of life, cost
Follow-up length	12 months
Notes	

Blue L, 2001

Participants	165 patients admitted with heart failure
Mean age	75 years
Male percentage	58%
Country	UK
Interventions	Patients in the usual care group were managed as usual by the admitting physician and, subsequently, general practitioner. They were not seen by the specialist nurses after hospital discharge. The nurse intervention consisted of a number of planned home visits of decreasing frequency, supplemented by telephone contact as needed. The aim was to educate the patient about heart failure and its treatment, optimise treatment (drugs, diet, exercise), monitor electrolyte concentrations, teach self monitoring and management (especially the early detection and treatment of decompensation), liaise with other health care and social workers as required, and provide psychological support. The nurses were given training in these roles before the start of the study. They used written protocols on the use of angiotensin converting enzyme inhibitors, diuretics, and digoxin in chronic heart failure and liaised with members of the department of cardiology as required. Participants were given a pocket sized booklet containing an explanation of heart failure and its treatment; dietary advice; contact details for the heart failure nurses; a list of their drugs, weights, and blood test results; and details of planned visits (dates and times).
Outcomes	All-cause mortality, hospital admission for Heart Failure
Follow-up length	12 months
Notes	

Bouvy M L,2003

Participants	152 patients with heart failure (predominantly New York Heart Association [NYHA] II and III)
Mean age	

Bouvy M L,2003

Male percentage	66%
Country	The Netherlands
Interventions	Cardiologists informed patients about the study. Patient's pharmacy and general practitioner (GP) were notified of their participation in the study. Pharmacists received training for the intervention that consisted of a structured interview on the patient's first visit to the community pharmacy after inclusion into study. A computerized medication history was used to discuss drug use, reasons for non-compliance — such as possible adverse drug reactions and difficulties to integrate medication use in daily life — to reinforce medication compliance. A short report of this interview was forwarded to the GP. Pharmacists then contacted patients on a monthly basis for a maximum of 6 months. Patients in the usual care group did not receive the structured interview or monthly follow-up.
Outcomes	Number of rehospitalizations, death, and quality of life,
Follow-up length	6 months
Notes	

Cline C M, 1998

Participants	190 patients admitted with heart failure
Mean age	76 years
Male percentage	52.3%
Country	Sweden
Interventions	First, patients and their families received an education programme on heart failure, describing its pathophysiology and pharmacological and non-pharmacological treatment. Adherence to prescribed medication was emphasised and patients were offered a seven day medication organiser (Dosett) if the study nurse considered one to be appropriate. Second, patients received guidelines for self management of diuretics based on the signs and symptoms of worsening heart failure (increased body weight, ankle oedema, dyspnoea, and fatigue) or fluid depletion (rapid weight loss). These data were registered in a patient diary (body weight, ankle circumference, and heart failure symptoms were regularly recorded). The education programme consisted of two 30 minute information visits by a nurse during primary hospitalisation and a one hour information visit for patients and family two weeks after discharge. In-hospital information on pathophysiology and self management guidelines were

Cline C M, 1998

	contained in the patient diary. The group information, held by a study nurse, employed an oral and video presentation to reinforce the information given in hospital. A special effort was made to inform family members who were present. Time was available for questions to the study nurse. Finally, patients were followed up at an easy access, nurse directed, outpatient clinic. The nurse was available by telephone during office hours and was able to see patients at short notice. There was only one prescheduled visit by the nurse at eight months after discharge. Patients were encouraged to contact the study nurse if: their diuretic adjustments did not ameliorate symptoms within two to three days; they felt unsure about which course of action to take; there were profound changes in self management variables; or at their discretion. The study nurses were registered nurses with experience of heart failure from coronary care units and clinical heart failure trials. They attended an overview lecture on heart failure before starting the study and were able to consult a cardiologist about specific patients at all times. They were also able to schedule doctors' vvisits as they considered appropriate. Intervention patients were offered outpatient visits with doctors at the department of cardiology at one and four months after discharge. The control group was followed up at the outpatient clinic at the department of cardiology, by either cardiologists in private practice or primary care physicians as considered appropriate by the discharging consultant. The treating physician was free to evaluate or treat as appropriate.
Outcomes	Mortality, hospitalization
Follow-up length	12 months
Notes	

DeBusk R F, 2004

Participants	462 patients hospitalised with a provisional diagnosis of CHF from Kaiser Permanente.
Mean age	72 years
Male percentage	51%
Country	USA
Interventions	Standardised telephonic physician directed nurse-managed case management, involving CHF lifestyle education and medication management. Patients contacted weekly for 6

DeBusk R F, 2004

	weeks, biweekly for 8 weeks and then monthly and bimonthly. Usual care not clearly defined, but was provided by the participating Kaiser Permanente medical centres, appeared to involve a high frequency of all of kinds of follow-up clinic visits (13 in 12 months following hospitalisation).
Outcomes	Mortality, rehospitalisation, emergency and outpatient department visits, prescription of recommended pharmacotherapy.
Follow-up length	12 months
Notes	Included in previous systematic review and meta-analysis Clark 2007a.

DeWalt D A, 2006

Participants	127 patients with confirmed HF, NYHA class II-IV symptoms within the last 3 months and currently taking furosemide from the University of North Carolina (UNC) General Internal Medicine Practice.
Mean age	62.5 years
Male percentage	47%
Country	USA
Interventions	Intervention patients received self-care education, picture-based educational materials with verbal explanation, a digital scale and scheduled follow-up phone calls (days 3, 7, 14, 21, 28, 56) and monthly during months 3-6 for reinforcement of education and revision of individualised care plan. Control group patients received a general heart failure education pamphlet and usual care from their primary physician (not specified). Data collection occurred at 6 and 12 months via in-person interview and medical record review.
Outcomes	Mortality, all-cause re-hospitalisation, HF-related quality of life, HF self-efficacy, HF knowledge, reported weight monitoring (self-management behaviour).
Follow-up length	12 months
Notes	

Doughty R N, 2002

Participants	197 patients with diagnosis of heart failure
Mean age	73
Male percentage	60
Country	New Zealand
Interventions	Patients randomized to the intervention group were scheduled

for an outpatient clinical review with the study team within 2 weeks of hospital discharge. At this initial clinic visit the patient's clinical status was reviewed, with particular attention to possible remediable exacerbating factors. One-on-one education with the study nurse was initiated at the first clinic visit. A patient diary, for daily weights, medication record, clinical notes and appointments, and education booklet were provided. A follow-up plan was devised for each patient aiming for 6-weekly visits alternating between the GP and heart failure clinic, although the patients were free to see their GPs at any time they wished. A detailed letter was faxed to the GP on the same day as the patient visited the heart failure clinic. This letter included summary comments outlining the rationale for any changes in treatment, and was followed-up with a phone call to the patient's GP to discuss any relevant changes in the management plan. The aim was for a close liaison between the patient and family, the GP and the hospital heart failure clinic. GPs made changes to the patient's management as they saw fit but were encouraged to discuss aspects of the patient's management with the clinic team at any stage. Subsequently, group education sessions (each lasting 1·5–2 h) were offered, two within 6 weeks of hospital discharge and a further after 6 months. These sessions were run by a cardiologist and the study nurse. The content of the one-on-one and group education included explanation of the symptoms and signs of heart failure, importance of monitoring of daily body weight and action plans should weight change, effects of medications and importance of compliance and recommendations regarding exercise and diet. The advice given was individualized and reinforced at each subsequent clinic visit by the study nurse. Monitoring of daily weights, with documentation in the diary and knowing what action to take should weight change, was reinforced at every available opportunity, either in the clinic or during phone calls with the patient. No assistance with travel costs or other incentives were provided for the patients in the intervention group.

The study team at the hospital heart failure clinic was available for consultation during normal working hours and received calls from both patients and their GPs. At times of worsening symptoms patients were initially advised to see their GP. No explicit criteria for readmission were pre-specified and the

Doughty R N, 2002

	decision to request admission rested with the GP. If admission was not required then an earlier heart failure clinic visit could be arranged. Patients randomized to the control group continued under the care of their GP with additional follow-up measures as usually recommended by the medical team responsible for their in-patient care.
Outcomes	Mortality, hospital readmission, quality of life
Follow-up length	12 months
Notes	

Dunagan W C, 2005

Participants	151 patients hospitalized with heart failure
Mean age	70 years
Male percentage	37%
Country	USA
Interventions	At enrollment, the program was described to each enrollee's primary physician and permission requested to adjust diuretic doses as needed, which was granted in 27 instances. Primary physicians were contacted directly about patients in either group with a Beck Depression Inventory (BDI) score suggesting possible depression or who answered affirmatively to questions concerning suicidal ideation. Patients in both groups received an educational packet describing the causes of HF, the basic principles of treatment, their role in routine care and monitoring of their condition, and appropriate strategies for managing a HF exacerbation. The intervention group received additional education from study nurses during scheduled telephone contact. Twenty patients also received 1 or more home visits, and 18 patients were provided bathroom scales. The intervention included regularly scheduled telephonic monitoring by specially trained nurses supervised by cardiologists specializing in HF. Calls were used to promote self-management skills, appropriate diet, and adherence to guideline-based therapy prescribed by primary physicians. Patients were encouraged to contact program nurses any time they experienced an increase in symptoms or had questions about their disease or treatment. During telephone contacts, nurses screened patients for HF exacerbations and administered a standardized screening instrument developed to

Dunagan W C, 2005

	detect such changes. If there was evidence of an exacerbation, program nurses recommended that the patient take supplemental diuretics or contacted the patient's physician for instructions. Patients were called within 3 days after hospital discharge or program enrollment and then at least weekly for 2 weeks. Call frequency subsequently was adjusted based on program nurses' assessments of patients' clinical status and self-management abilities.
Outcomes	Mortality, readmission
Follow-up length	12 months
Notes	

Ekman I, 1998

Participants	192 patients with heart failure hospitalzed
Mean age	76 years
Male percentage	55%
Country	Canada
Interventions	Usual care for hospital-to-home transfer involves completion of medical history, nursing assessment form, and, in ideal circumstances within 24 hours of hospital admission, a multidisciplinary discharge plan. Weekly discharge planning meetings further identify patient needs. A regional home care co-coordinator consults with the hospital team as required and may meet directly with patients and families. Immediately before discharge, a physician completes a referral for home care, and necessary services and supplies are communicated to the home nursing agency. Usual home nursing care for CHF patients includes assessment and monitoring, health teaching, provision of direct care, eg, administration of medications, and managing equipment and treatments. Patients in the Intervention Group (Transitional Care - TC) arm received the standard discharge planning and care, plus a comprehensive program, adding supports to improve the transfer from hospital to home. To develop this program, hospital and community nurses met to focus on the 'outreach' from the hospital and 'in-reach' from the community during the transition. An intersectoral continuity of care framework guided their efforts in identifying gaps to specifically address 3 major aspect of a hospital-to-home transition: (1) supportive care for self-management; (2) linkages between hospital and home nurses and patients; and (3) the balance of care between

Ekman I, 1998

	the patient and family and professional providers. The defining characteristics of TC were the use of a structured, comprehensive, evidenced-based protocol for counselling and education for heart failure selfmanagement, plus additional and planned linkages to support individuals in taking charge of aspects of their care. An evidence-based intervention is defined as care based by current research or, in the absence of strong empirical findings, on expert consensus. This may involve the use of professional practice standards and practice guidelines, if available. The education-counseling protocol entitled, Partners in Care for Congestive Heart Failure (PCCHF), was developed in response to AHCPR guideline recommendations. PCCHF has two clinical components: (1) the patient workbook, and (2) an education map that provided the overall education plan, and serving as a patient-held documentation tool. The workbook, a comprehensive resource for self-management, provides a structured approach for patient education, yet allows for tailoring to individual needs. It covers the basics of heart function and self-monitoring, what CHF means, management of medications, diet, exercise, stress, support systems, and community resources. There is a pocket for inserting patient-specific information (eg, medication, dietary handouts). Linkages, additional to usual practice, were created among providers and the patients including: a nursing transfer letter to the home care nurse detailing clinical status and selfmanagement needs; a telephone outreach from the hospital nurse within 24 hours of discharge; notification to home care as to whom hospital primary nurse was for follow-up consult if necessary; and a patient-held documentation tool.
Outcomes	Readmission, quality of life
Follow-up length	12 weeks
Notes	

Galbreath A D, 2004

Participants	1069 patients with symptoms of CHF and documented systolic (mean EF 35%) or diastolic dysfunction (echo confirmed).
Mean age	71 years
Male percentage	71 %
Country	USA
Interventions	All intervention patients received bathroom scales and were

Galbreath A D, 2004

	designated a disease manager who administered the disease management program telephonically. Initial call frequency was weekly then transitioned to monthly for the duration of the study. Call frequency could be adjusted for acuity or need. After each call a call summary was faxed to the patients primary care provider. An additional randomisation was performed within the intervention arm, with some participants provided with in-home technology (BP monitor, pulse oximeter) – these measurements were reported by the patient to the disease manager, but the data were not forwarded to the primary care provider. These patients also wore activity monitors at regular intervals and had six-monthly measurement of thoracic bioimpedance cardiac output - these data were not forwarded to the primary care physician. The authors state: "because data derived from the technology were not used in clinical management, we combined results from the two treatment groups for the purposes of this analysis." Traditional care patients were managed as usual by their physicians.
Outcomes	All-cause mortality, six-min walk performance, functional therapeutic class improvement, total healthcare costs. Improvement in ejection fraction improvement and medication adherence were assessed in a subgroup.
Follow-up length	18 months
Notes	

Gattis W A, 1999

Participants	Participants 181 patients with heart failure being evaluated in cardiology clinic.
Mean age	67 years
Male percentage	68%
Country	USA
Interventions	Clinical pharmacist-led medication review and patient education. Regularly scheduled telephone contact (at two, 12 and 24 weeks) to detect clinical deterioration early. The control group received usual care which did not include the pharmacist providing recommendations regarding drug therapy to the attending physician or providing education to

Gattis W A, 1999

	the patient. Patient assessment and education were provided by the attending physician and/or physician assistant or nurse practitioner. The patient was contacted by the pharmacist via telephone to identify clinical events.
Outcomes	Mortality, rehospitalisation, medication prescription.
Follow-up length	6 months
Notes	Included in previous systematic review and meta-analysis Clark 2007a.

Hughes S L, 2000

Participants	30 patients with Heart Failure
Mean age	No available descriptive data for HF patients
Male percentage	No available descriptive data for HF patients
Country	USA
Interventions	The treatment incorporated key features of integrated networks, including systematic screening to identify high risk patients, an emphasis on continuity of care, and the management of patients across organizational boundaries. Participating sites were asked to provide continuous patient care management with the home-based care physician serving as the primary care physician. Patients continued to receive homecare for as long as needed, until maximum patient benefit was achieved, or until a different level of care was required. Sites used clinical judgment to provide visits based on patient condition and need.
Outcomes	Patient functional status, patient and caregiver HRQoL and satisfaction, caregiver burden, hospital readmissions, and costs
Follow-up length	12 months
Notes	

Jaarsma T, 1999

Participants	179 patients hospitalized with heart failure
Mean age	73 years
Male percentage	58%
Country	Netherlands
Interventions	The supportive–educative intervention consisted of intensive, systematic and planned education by a study nurse about the consequences of heart failure in daily life, using a standard

Jaarsma T, 1999

	nursing care plan developed by the researchers for heart failure patients in older age. Important topics were discussed with every patient, for example, recognition of warning symptoms of worsening heart failure, sodium restriction, fluid balance, and compliance. In addition, individual problems were discussed, for example problems in social interaction, sexual function or limited access to the general practitioner. During hospital stay, the study nurse assessed the patients' needs, provided education and support to the patient (and family), gave the patient a card with warning symptoms and discussed discharge. Within 1 week after discharge the study nurse telephoned the patient to assess potential problems and to make an appointment for a home visit. During the home visit the study nurse reinforced and continued education as warranted by the patient situation. If needed, the information was given to a carer about specific patient needs. Between discharge and the home visit, patients could call the study nurse in case of problems. After the home visit, the patient was advised to call their cardiologist, general practitioner or emergency heart centre in case of difficulties. The intervention lasted from hospital admission to 10 days after discharge from hospital. Patients assigned to the care as usual (control group) received all standard care. This meant that they were not provided with structured patient education, a follow-up telephone call or a home visit by a nurse. Dependent on the insight of an individual nurse or physician the patient received information (in writing or oral) about medication and lifestyle. Patients from the control and intervention groups were never assigned to the same room on the nursing unit. The two study nurses were involved in data collection as researcher and research assistant. However, the person who collected the data and the nurse who visited the patient for the intervention were never the same.
Outcomes	Mortality, readmission, hospital staying
Follow-up length	9 months
Notes	

Kasper E K, 2002

Participants	200 patients hospitalized with Chronic Heart Failure
Mean age	64 years (median)

Kasper E K, 2002

Male percentage	60%
Country	USA
Interventions	Intervention group. The four members of the intervention team were the telephone nurse coordinator, the CHF nurse, the CHF cardiologist and the patient's primary physician. The telephone nurse coordinator made follow-up calls to patients from a central site located in Rockville, Maryland. Telephone calls were placed within 72 h of hospital discharge, then weekly for one month—twice in the second month and monthly thereafter, unless a problem occurred that required more frequent contact. The telephone nurse coordinator followed a set script and pursued problems as clinically indicated, but did not adjust medications over the telephone. The CHF nurses were assigned to assist the intervention group and helped to implement the therapeutic plan designed by the CHF cardiologists. Patients had at least monthly follow-up with these nurses. Most visits occurred in CHF clinics located at each site, but some occurred in the patient's home. The CHF nurses adjusted medications under the directions of the CHF cardiologists, following a prespecified algorithm, which included initiation and titration of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and diuretics. The algorithm included a 2-g sodium-restricted diet, as well as a recommendation to exercise by walking for 20 min at least four days per week. The treatment plan was individualized for each patient. In the course of the study, the algorithm was updated to include, for example, the use of beta-blockers. All members of the team, except for the patients' primary physicians, participated in weekly patient care meetings. The CHF cardiologists designed and documented a treatment plan for all study patients before randomization and saw the patients at baseline and six months. They designed the prespecified algorithm according to available CHF guidelines and clinical experience. The primary physicians approved of their patients' participation, as well as medication, dietary, activity and follow-up regimens. They managed all problems not related to CHF, received regular updates from the CHF nurses and were notified of abnormal laboratory values. Patients in the intervention group with limited financial resources were provided, if needed, a scale, a 3-g sodium "Meals on Wheels" diet, medications, transportation to the

Kasper E K, 2002

	clinic and a telephone. All patients in the intervention group were supplied with a pill sorter, a list of correct medications, a list of dietary and physical activity recommendations, a contact number available 24 h/day and patient education material. Patients assigned to the non-intervention group were cared for by their primary physicians. The baseline therapeutic plan designed by the CHF cardiologist was documented in the patient's chart, without further intervention.
Outcomes	death, CHF hospital admissions, total hospital admissions, changes in quality of life and activity status.
Follow-up length	Six months
Notes	

Krumholz H M, 2002

Participants	88 patients hospitalized with heart failure
Mean age	74 years
Male percentage	57%
Country	USA
Interventions	The study intervention was based on five sequential care domains for chronic illness, including patient knowledge of the illness, the relation between medications and illness, the relation between health behaviours and illness, knowledge of early signs and symptoms of decompensation and where and when to obtain assistance. In the teaching module, each sequential domain supplemented knowledge acquired in previous domains. Operationalizing the intervention occurred in two phases. Initially, the patients' understanding of the domains was assessed and reviewed in order to provide information about patient gaps in knowledge for the nurse to address. Subsequent follow-up sessions reviewed knowledge of care domains and provided support for patients to apply their knowledge, participate in managing these domains and effectively seek and access care. This support was designed to reinforce the initial educational foundation theoretically by empowering patients and offering strategies to improve patients' compliance. For the initial phase, an experienced cardiac nurse educated patients during an hour-long face-to-face in-depth session within two weeks of hospital discharge using a teaching booklet. Home visits were performed for 45% of intervention patients unable to travel to the hospital, but the visits were not

Krumholz H M, 2002

	intended to provide additional assessments that were more detailed than clinic sessions. Neither clinical assessment of HF nor modification of current medical regimen was a component of the baseline meeting. During the subsequent telemonitoring phase, the nurse contacted the patient by phone on a weekly basis for four weeks, then biweekly for eight weeks and then monthly for a total intervention period of one year. These calls reinforced care domains but did not modify current regimens or provide recommendations about treatment. However, the nurse could recommend that the patient consult his or her physician when the patient's status deteriorated abruptly or the patient experienced a significant problem with medical therapy requiring prompt attention, and, in doing so, the nurse helped patients understand when and how to seek and access care. Patients assigned to the control group received all usual care treatments and services ordered by their physicians.
Outcomes	Mortality, readmission, days of hospitalization
Follow-up length	12 months
Notes	

Mejhert M, 2004

Participants	208 patients with heart failure
Mean age	75 years
Male percentage	58%
Country	Sweden
Interventions	A senior cardiologist supervises the intervention programme. After referral to the programme, the patient pays regular visits to the outpatient clinic and is encouraged to keep in contact with the nurse. At each visit the nurse checks symptoms and signs of heart failure, blood pressure, heart rate, and weight. Laboratory tests measure creatinine, sodium, and potassium concentrations. Nurses working in the programme are allowed to institute and change the doses of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, beta enoceptor blockers, potassium substitution, diuretics, and potassium sparing diuretics according to a standard protocol. The patient is instructed to check his or her weight regularly and to monitor early signs of deterioration. Patients with good compliance are instructed to change dosing of diuretics on their own. Dietary advice recommends restricted sodium, fluid, and alcohol intake. Information is repeated in booklets and

Mejhert M, 2004

	computerised educational programmes. According to the routine, written information is given in a structured format to the general practitioner at discharge of a patient from our institution. Patients randomised to the control group typically were followed up by their general practitioners to be treated according to the local health care plan for heart failure. If left ventricular systolic function is reduced, with an ejection fraction , 40%, an ACE inhibitor should be initiated. Several meetings with hospital specialists and general practitioners have addressed the importance of optimised medication and education of patients with heart failure. In addition to the visits outlined above, all patients were scheduled for clinical examinations and detailed control of medication at 6, 12, and 18 months. One and the same cardiologist met the patients at all visits. The patients were informed at the start of the study that these visits were purely observational and with no intention to initiate examinations or to change medication.
Outcomes	Hospitalization, mortality, quality of life
Follow-up length	18 months
Notes	

Naylor M D, 2004

Participants	142
Mean age	76 years
Male percentage	49%
Country	USA
Interventions	Patients in the control group received the hospital's routine discharge plan, which is used for patients of all ages and diagnostic classifications. Criteria-based screening of all hospital admissions normally occurred within 48 hours of admission. Uncomplicated discharges were managed by the patient's physician and primary nurse. Complicated discharges, which necessitated coordination of services and external providers, involved social workers and community nursing coordinators employed by the hospital. Discharge planning services were provided in accordance with the medical plan of care. Patients and caregivers in the intervention group received the hospital's routine plan and a comprehensive, individualized discharge planning protocol developed specifically for elderly

patients and implemented by gerontologic clinical nurse specialists. The protocol extended from hospital admission to 2 weeks after discharge. Compared with the hospital's routine procedure, the discharge planning protocol included the following unique features: 1) comprehensive initial and ongoing assessment of the discharge planning needs of the elderly patient and his or her caregiver; 2) development of a discharge plan in collaboration with the patient, caregiver, physician, primary nurse, and other members of the health care team; 3) validation of patient and caregiver education; 4) coordination of the discharge plan throughout the patient's hospitalization and through 2 weeks after discharge; 5) interdisciplinary communication regarding discharge status; and 6) ongoing evaluation of the effectiveness of the discharge plan.

Two half-time nurse specialists with master's degrees in gerontologic nursing and a minimum of 1 year of practice as a nurse specialist were hired to implement the comprehensive discharge planning protocol for patients in the intervention group. Within 24 to 48 hours of admission, the nurse specialist visited the patient and contacted the caregiver to complete the initial patient and caregiver assessment and to document the preliminary discharge plan.

The nurse specialist visited the patient every 48 hours thereafter to implement the plan through patient and caregiver education, referrals, consultation with health care team members, counseling, and coordination of home services. The final visit was made within 24 hours of discharge to finalize discharge preparations. Summaries of the discharge plan were recorded in the patient's chart and distributed to the patient, primary care physician, and other health care team members who would care for the patient at home.

In addition to personal visits, the nurse specialist was available 7 days a week by telephone (8 a.m. to 10 p.m. on weekdays; 8 a.m. to l2p.m. on weekends) throughout the patient's hospitalization and for 2 weeks after discharge for any questions or concerns from the patient, caregiver, or health care team member that were relevant to the discharge plan. The nurse specialist also initiated a minimum of two telephone calls during the first 2 weeks after discharge to monitor the patient's progress and intervene when necessary.

Naylor M D, 2004

Outcomes	length of initial hospital stay, length of time between initial hospital discharge and readmission, and rehospitalization rates
Follow-up length	12 weeks
Notes	

Peters-Klimm F, 2010

Participants	197 patients with ascertained left ventricular systolic dysfunction
Mean age	70 years
Male percentage	73%
Country	Germany
Interventions	Patients randomised to the intervention received complex, structured case management by a trained doctor's assistant (DA): The design of the intervention addressed the 4 of the 6 elements of the CCM (delivery system design, self-management support, decision support, clinical information systems): DAs completed 6 hours of theoretical and practical training before conducting regular patient monitoring for 1 year by telephone (patients with NYHA functional status III or IV three-weekly versus I or II six-weekly) and by 3 home visits for all patients. DAs gave feedback of the results of the monitoring and screening to their employing GP. The programme included the use of a CPG, a patient leaflet according to the national CPG, booklets and tailored diaries.. Additionally, GPs received graphically depicted individual performance feedback on evidence-based pharmacotherapy (from data of baseline documentation). For patients in the control (usual care) group, no case management was applied.
Outcomes	Quality of life and hospital admission
Follow-up length	12 months
Notes	

Philbin E F, 2000

Participants	1504 patients admitted with heart failure
Mean age	76 years
Male percentage	44%
Country	USA
Interventions	Physicians and nurse leaders and administrators responsible for quality management at the intervention hospitals participated in the leadership of this study and served as

Philbin E F, 2000

	champions for the project at their institutions. The quality improvement intervention attempted to maximize the implementation of an inpatient critical pathway for heart failure management, which was designed by the study leadership. Its format was a Gantt chart or timetask matrix. The pathway recommended diagnostic tests and treatments that were considered to be highly indicated based on published clinical trial results, expert guidelines, or wide acceptance as current standards, but omitted those considered experimental or controversial. Standardized admission orders, which supplemented the pathway, were also made available. In addition, we provided several other components aimed at improving provider and patient knowledge, expediting diagnosis and treatment, and reducing readmission. These included a critical pathway for use in the emergency department, which emphasized rapid diagnosis of heart failure and initiation of intravenous diuretic therapy, and a home care pathway for use by home health personnel after hospital discharge. An experienced consulting firm (The Center for Case Management, Natick, Massachusetts) assisted in implementation of the pathways and other components of the intervention. Three medical grand rounds were given at each hospital by regional or national experts in heart failure, and five lectures about clinical issues in heart failure were provided for nurses and other health professionals at each hospital. Videotapes of all eight lectures were available to assist in dissemination of the didactic message. Teaching aids were given to patients and their families. Finally, comprehensive hospital-specific performance and benchmarking reports about process and outcomes of care from the baseline period were presented to the intervention hospitals orally and as a written 45-page report as catalysts for changes in clinical practice.
Outcomes	Mortality, hospitalization and quality of life
Follow-up length	6 months
Notes	

Rainville E C 1999

Participants	38 patients aged ≥ 50 years discharged from hospital with heart failure.
Mean age	70 years

Rainville E C 1999

Male percentage	50%
Country	USA
Interventions	Usual care plus a pharmacist-led medication review, patient education, medication management prior to discharge and at Day 3, Day 7, 30 days, 90 days and 12 months via telephone. Usual care consisted of routine care and preparation for discharge including written prescriptions, physician discharge instructions and a nurse review of diet, treatment plans and medications. The nurses provided the patient with computer generated drug information sheets. Patients were contacted by a pharmacist at 30 days, 90 days and 12 months to determine readmissions.
Outcomes	Mortality, rehospitalisation, functional assessment score.
Follow-up length	12 months
Notes	Included in previous systematic review and meta-analysis Clark 2007a.

Rich M W, 1993

Participants	98 patients admitted with congestive heart failure
Mean age	79 years
Male percentage	41%
Country	USA
Interventions	Nurse-directed multi-disciplinary intervention including comprehensive education of the patient and family, a prescribed diet, social service consultation planning for early discharge, a review of medications by a geriatric cardiologist, and intensive follow-up through the hospital's home care services, supplemented by individualised home visits and telephone contact.
Outcomes	Readmission
Follow-up length	3 months
Notes	

Riegel B, 2002

Participants	358 patients discharged from hospital with heart failure.
Mean age	74 years
Male percentage	49%
Country	USA
Interventions	Telephonic case management by a registered nurse using decision support software, involving patient education and

Riegel B, 2002

	counselling and liaison with primary care physician. Patients were telephoned within 5 days of discharge and thereafter at a frequency guided by the software and case manager (mean 17 calls). Usual care was not standardised, and no formal telephonic case-management was in existence at these institutions. These patients presumably received some education regarding HF management prior to hospital discharge.
Outcomes	Mortality, rehospitalisation, physician and emergency department visits, inpatient costs, patient satisfaction.
Follow-up length	Six months
Notes	Included in previous systematic review and meta-analysis Clark 2007a.

Riegel B, 2006

Participants	135 hospitalized Hispanic patient with CHF
Mean age	72 years
Male percentage	46%
Country	USA
Interventions	Education, monitoring and guidance by bilingual-bicultural Mexican-American registered nurses via telephone case management standardised using decision support software. Patients were contacted on average within 5 days of discharge and thereafter at a frequency guided by the software and nurse case manager over a 6 month period (mean 13.5 calls to patients and 8.4 additional calls to families). Printed educational material was provided monthly and upon request in the relevant language. Usual care was not standardised and no formal disease management program existed at these institutions. The standard of usual care was that patients were educated regarding HF management before discharge, assuming that the nurse spoke the patient's language or someone bilingual was available to translate. In reality, only a small portion of staff were bilingual.
Outcomes	Mortality, re-hospitalisation, cost of care, self-reported health-related quality of life and depression.
Follow-up length	Six months
Notes	Included in previous systematic review and meta-analysis Clark 2007a.

Sisk J E, 2006

Participants	Participants 406 non-Hispanic and Hispanic patients with documented systolic dysfunction.
Mean age	59 years
Male percentage	54%
Country	USA
Interventions	An in-person appointment was arranged for each intervention patient, which included symptom and disease education and referral to additional patient services (if required). Follow-up telephone calls consisted of patient assessment, recording of admission information reinforcement of self-monitoring and administration of a food-frequency questionnaire (at 2, 4, 8, 12 and 24 weeks and a report sent to patients). Intervention nurses coordinated flow of information between patient and clinician and arranged medication adjustment and required examinations. Usual care patients received guidelines for managing systolic dysfunction, but no other care information was specified.
Outcomes	Mortality, hospitalisations, functional status (including quality of life).
Follow-up length	12 months
Notes	

Stewart S 2002

Participants	297 patients with congestive heart failure
Mean age	75
Male percentage	84%
Country	Australia
Interventions	Patients assigned to intervention group, while receiving the same level of care as those assigned to "usual care," received a structured home visit within 7 to 14 days of discharge. The fundamental aim of intervention is to optimize the management of the patient's chronic disease state(s) and to facilitate the rapid recognition and treatment of potential problems. Initial assessment included a physical examination and a review of the patient's adherence to, and knowledge of, prescribed treatment and their social support system, in addition to identification of any other factors likely to increase the probability of readmission or death. A report (with recommendations) was sent to the patient's treating physicians and a combination of short- and long-term strategies applied. The nurse played a pivotal role in both studies by coordinating

Stewart S 2002

	efforts to optimize the patient's management and providing a critical link to the appropriate health care if problems arose.
Outcomes	Mortality, hospitalization, healthcare cost
Follow-up length	4.2 years (median)
Notes	

Stromberg A, 2003

Participants	106 Patients hospitalized with heart failure
Mean age	78 years
Male percentage	52%
Country	Sweden
Interventions	The patients in the intervention group were followed up at a nurse-led heart failure clinic staffed by specially educated and experienced cardiac nurses, delegated the responsibility for making protocol-led changes in medications. The first visit was scheduled 2–3 weeks after discharge. All visits lasted for 1 h and the nurse evaluated the status and if the heart failure treatment was optimised, gave education about heart failure and social support to the patient and his family. The status taken during the visit included anamnesis, auscultation of heart and lungs and inspection of oedema. If treatment needed to be optimised, the cardiologist with medical responsibility for the heart failure clinic was consulted and treatment changed in accordance with current clinical guidelines. For example the dose of the ACE-inhibitor and/or beta-blocker could be increased if reaching the target-dose or highest tolerable dose was not done during hospitalisation. The education was individualised, included both written and verbal information and was based on guidelines. The patients and their families were educated on heart failure and the content included definition and symptoms/signs of heart failure, aetiology, rationale for treatment and drug counselling. It also included non-pharmacological treatment with dietary changes such as restricted fluid, sodium and alcohol intake, individually adjusted energy intake in order to reduce overweight or prevent malnutrition, smoking cessation, exercise in stable heart failure and infection prophylaxis with vaccinations. The nurses adjusted the education to previous knowledge, educational level and cognitive function of the patient. The education specially aimed at assisting patients to improve their self-care regimen e.g. maintain a flexible regimen with loop-

Stromberg A, 2003

	diuretics, restrict the intake of fluids and sodium and monitor symptoms such as weight gain, increased breathlessness and oedema daily. Another important component of the nursing intervention was to provide psychosocial support by creating a supporting relationship between the nurse and the patient. The patients could contact the nurses at the heart failure clinics during daily telephone hours (8 a.m.–5 p.m. during weekdays) and the heart failure nurses called patients in order to provide psychosocial support, evaluate drug changes or other actions taken due to deterioration and side effects. If the patient was unstable with symptoms of worsening heart failure at the time of the follow-up visit or if further education was needed, the patient was scheduled for another visit to the heart failure clinic. When the patients were stable and well informed, they were referred back to their general practitioner in primary health care. All patients in the control group were managed in accordance with current clinical practice and received conventional follow-up in primary health care. The responsible physicians in the primary health care were free to evaluate and treat the patient according to their own judgement. Some patients got a scheduled visit after discharge, but most patients were encouraged to phone primary health care if they had problems due to heart failure. There were no specialised heart failure nurses, no standardised education or structured follow-up for patients with heart failure at any of primary health care centres.
Outcomes	Mortality, number of readmissions for any reason, number of days in hospital and self-care behaviour.
Follow-up length	12 months
Notes	

Thompson DR, 2005

Participants	106 patients admitted with Chronic Heart Failure
Mean age	73 years
Male percentage	73%
Country	UK
Interventions	The patients allocated to the UC group received standard care (i.e. explanation of their condition and prescribed medications by the ward nurse and referral to appropriate post-discharge support as required). Patients were given an outpatient

Thompson DR, 2005

	department appointment 6–8 weeks post discharge according to individual consultant practice. The study intervention was primarily applied by two nurses experienced in the management of heart failure and with postgraduate qualifications, using strict treatment protocols. As such, patients allocated to intervention group were seen by the study specialist nurses prior to their discharge and received a home visit within 10 days of hospital discharge. At the ward visit, patients received information on their condition, medications and what to expect when they went home. An appointment was arranged at a time of the patient's convenience for the home visit. In addition, the patient was given a card with a contact telephone number for the specialist nurse (office hours only) where messages could be left regarding any questions or queries the patient or their family may have. At the home visit, patients (and their family if appropriate) received education on their condition, including symptom recognition, symptom management and lifestyle issues. A thorough clinical examination, involving a review of their clinical history since hospital discharge, functional status, vital observations, heart and lung sounds and hydration status was also performed. All patients accepted an invitation to attend a monthly nurse-led outpatient heart failure clinic for at least 6 months post discharge. However, concomitant illness (e.g. influenza), early post discharge death and the logistics of travelling to the clinic meant that only 79% of the patients attended all their clinic sessions. During the clinic visits patients (and their family if appropriate) received a full educational package, including diagnosis, symptom recognition, symptom management, lifestyle issues and crisis management. A clinical examination (see above) was performed to assess cardiac status and fluid retention. Weight, electrolytes, renal, hepatic function and blood counts were monitored. New therapeutic agents (e.g. Spironlactone) were also commenced according to local protocol based upon the Taskforce Recommendations of the European Society of Cardiology (2000) and the Scottish Inter Collegiate Guidelines (1999). Where appropriate, referral to other local health and social services was made.
Outcomes	Hospital stay, mortality, quality of life
Follow-up length	6 months
Notes	

Tsuyuki R T, 2004

Participants	276 patients discharged from hospital with heart failure.
Mean age	72 years
Male percentage	58%
Country	Canada.
Interventions	Early discharge planning with provision of adherence aids, patient education, regularly scheduled telephone contact with local research coordinator at two and four weeks then monthly thereafter for six months. Recommendations to see primary care physician if not on target dose ACE inhibitor or deterioration. Patients assigned to usual care received a general heart disease pamphlet before discharge, but no formal counselling beyond what was routine at the hospital. Patients were contacted monthly for six months to ascertain clinical events.
Outcomes	Mortality, re-hospitalisation, medication adherence, physician and emergency department visits, cost-analysis.
Follow-up length	Six months
Notes	Included in previous systematic review and meta-analysis Clark 2007a.

Wakefield B J,2008

Participants	148 patients hospitalised for HF exacerbation.
Mean age	69 years
Male percentage	99%
Country	USA
Interventions	Patients allocated to the intervention group were allocated to 1 of 2 interventions: telephone follow-up or videophone follow-up. Intervention patients were contacted by a nurse 3 times in the first week then weekly for 11 weeks. Symptoms and the patients discharge plan was reviewed and reinforced as well as referrals made if required. Additionally, the intervention nurses employed behaviour skill training strategies tomaximise self-management, self-monitoring and self-efficacy. Usual care was not specified except to state that “subjects contacted their primary care nurse case manager by telephone if needed”.
Outcomes	Mortality, readmissions, hospital days, time to first readmission, urgent care clinic visits, quality of life, intervention dose and technical issues.
Follow-up length	12 months

Wakefield B J,2008

Notes	Telephone and video-telephone intervention arms were combined and classed as disease management program

Weinberger M, 1996

Participants	504 patients
Mean age	98%
Male percentage	63
Country	USA
Interventions	The intervention was delivered by a team consisting of one licensed registered nurse and one primary care physician. The intervention had both an inpatient component, which began immediately after randomization, and an outpatient component, which began at discharge. Control Group The care of patients in control group after discharge could be provided by community physicians or at Veterans Affairs clinics, as arranged by the physicians treating them as inpatients. The control patients did not have access to the primary care nurse and received no supplemental education or assessment of needs beyond what was customarily offered at each site.
Outcomes	Readmission, length of hospital stay, quality of life
Follow-up length	6 months
Notes	

Young W, 2003

Participants	715 consecutive patients admitted with elevated cardiac markers
Mean age	69 years
Male percentage	70
Country	Canada
Interventions	The DMP included 6 home visits by a cardiac-trained nurse, a standardized nurses' checklist, referral criteria for specialty care, communication with the family physician and patient education.
Outcomes	Readmission days
Follow-up length	1000 days
Notes	

2.2 *Telemedicine services: home-monitoring*

Home-monitoring (HM) services are models in which the disease management is integrated with remote monitoring of signs, symptoms, physiological parameters or biomedical signals. This implies that HM is generally a more complex model than DMP, requiring the use of more complex technologies. In literature there are many different models of Home Monitoring (HM)[12].

From a literature research (for details about the keywords adopted see section 2.3), 11 randomized clinical trials (RCTs) comparing HM and usual care in patients suffering from CHF were identified. The most important information of these studies were reported in the Table 2

Table 2: characteristics of the studies comparing Home-Monitoring with Usual Care

Antonicelli R, 2008	
Participants	57 patients hospitalised for worsening symptoms and signs of CHF with NYHA class II-IV, evidence of pulmonary congestions on chest x-ray and EF < 40%. Patients with NYHA class II-III with an EF > 40% and diastolic LV dysfunction were also included.
Mean age	78 years.
Male percentage	61%
Country	Italy
Interventions	Patients randomised to home telemonitoring-based care were contacted by telephone at least once a week to collect information on symptoms and treatment adherence as well as BP, HR, weight and 24h urine output on the previous day. A weekly ECG transmission was also obtained. Patients were then evaluated and their regimen altered when necessary based on this data. Additionally, clinic visits were performed when required based on the data collected or telephone interviews. Usual care involved receiving standard care based on routinely scheduled clinic visits (every four months) performed by a team specialized in CHF patient management. These subjects were also contacted monthly by telephone to collect data on new hospital admissions, complications and death. Additional clinic visits were performed whenever required when clinical

Antonicelli R, 2008

	status altered
Outcomes	Combined rate of mortality and hospitalisation, these rates considered individually, quality of life
Follow-up length	12 month
Notes	

Balk A H, 2008

Participants	214 patients with CHF NYHA class I-IV
Mean age	66 years
Male percentage	70%
Country	The Netherlands
Interventions	Patients in the Intervention group were provided a MOTIVA system (TV-channel providing educational material, reminders of medication, health related surveys and motivational messages to encourage the prescribed lifestyle regimen) in addition to scheduled cardiologist appointments. A subgroup of intervention patients also received automated BP and weight devices that automatically communicated readings via the telephone (those who had been hospitalised in the prior year for HF). Patient guidance followed a personalised plan. Control subjects were followed by their cardiologists and HF-nurses according to standard local practice. All patients recorded all contacts with healthcare professionals and hospital admissions.
Outcomes	All-cause hospital days per year, days alive and out of hospital, quality of life, knowledge of disease, self-care.
Follow-up length	288 days (mean value)
Notes	

Bourge R C, 2008

Participants	274 patients with CHF NYHA class III or IV, who received an implantable continuous hemodynamic monitor
Mean age	58 years
Male percentage	65%
Country	USA
Interventions	All patients received the ICHM system (Model 9520, Medtronic) and optimal medical therapy. The ICHM system consists of: 1) a programmable device that processes and stores information and is similar in appearance to the pulse generator of a pacemaker; and 2) a transvenous

Bourge R C, 2008

	lead (model 4328A, Medtronic) that has a sensor incorporated near its tip to measure intracardiac pressure. The implantation procedure is similar to that of a single-lead pacemaker system, with the device positioned subcutaneously in the pectoral area and the lead positioned transvenously in the right ventricular outflow tract or septum. It is capable of continuously monitoring and storing heart rate, body temperature, patient activity, right ventricular systolic and diastolic pressure, maximal positive and negative rate of change in right ventricular pressure (dP/dt), right ventricular pre-ejection and systolic time intervals, and estimated pulmonary arterial diastolic pressure (ePAD). The hemodynamic information from the monitor was used to guide patient management only in the treatment group
Outcomes	HF-related hospitalization, emergency department access,
Follow-up length	6 months
Notes	

de Lusignan S 2001

Participants	20 patients with heart failure confirmed by cardiologist, identified from the database of an academic general practice.
Mean age	75 years
Male percentage	not specified
Country	UK
Interventions	Telemonitoring of vital signs (pulse, BP, weight) and clinical status daily assessed daily by nurses along with video consults with a nurse weekly for three months, fortnightly for three months, then monthly. Usual care consisted of standard general practice treatment; in addition they had their pulse, BP and weight measured quarterly. They were evaluated in the same manner as the intervention group
Outcomes	Mortality, compliance with intervention and medication, patient satisfaction, quality of life
Follow-up length	12 months
Notes	Included in previous systematic review and meta-analysis Clark 2007a.

Giordano A, 2009

Participants	460 confirmed CHF patients with LVEF < 40% and at least one hospitalisation for acute HF in the prior year.

Giordano A, 2009

Mean age	57 years
Male percentage	85%
Country	Italy
Interventions	Home-Based Telemanagement (HBT) patients received a one-lead trace portable device that transferred results via telephone where a nurse was available for interactive teleconsultation. Scheduled standardised telemonitoring appointments were performed every week to 15 days depending on HF severity discussing symtomology, medications, self-care and, if required, the transmission of the ECG trace. Usual care consisted of patients being referred to their primary care physician (PCP) and cardiologist for clinical management. These patients attended a two-weeks post-discharge PCP appointment and a structured follow-up outpatient cardiologist appointment at 12 months.
Outcomes	Unplanned cardiovascular hospital readmissions, hospitalisation for HF, haemodynamic instability episode occurrence, cardiovascular mortality.
Follow-up length	12 months
Notes	

Goldberg L R, 2003

Participants	280 patients hospitalised with NYHA Class III-IV, with a LVEF < 35%.
Mean age	59 years
Male percentage	68%
Country	USA
Interventions	Daily transmission of weight and symptoms using a customised monitor, data was reviewed daily by nurses and concerns reported to the physician. Patients in the control group were instructed to contact their physician for weight increases of more than a pre-specified amount or if their symptoms of heart failure worsened. They had a weight log to bring to visits. Follow-up visits, other than study visits were at the discretion of the treating physician. Telephone contacts were permitted at the discretion of the treating physician or nurse.
Outcomes	Mortality, rehospitalisation, emergency department visits, quality of life, patient satisfaction, compliance with intervention.
Follow-up length	Six months

Goldberg L R, 2003

Notes

Kashem A, 2008

Participants	48 patients with CHF NYHA class II-IV
Mean age	53 years
Male percentage	74%
Country	USA
Interventions	For all patients care is guideline-based with tailored medication therapy based on the patient's clinical status, comorbidities, drug tolerance, age, and ethnic background. All patients were given a digital sphygmomanometer, a pedometer, and a scale when needed. They were instructed on their use and encouraged to self-monitor at home. These devices were typical off-the-shelf device available in most pharmacies. The patients recorded their blood pressure, body weight, and total number of steps/day in a logbook and manually entered their blood pressure, weight using calibrated scale, and steps data information through the secure Web site. All patients received the present standard care provided by advanced HF and cardiomyopathy program.. Each patient in the treatment group was instructed on how to use the telemedicine system. The patient was then instructed to send data from home within 2 days. Because the telemedicine system was designed for maintenance care and not for emergency care, patients using the system were instructed to either call the practice on-call number or report to the nearest hospital if they needed urgent or emergency care. Blood pressure, pulse, steps/day, and weight together with symptoms were entered. The most recent laboratory data and medication were entered by the practice staff, and the patient was instructed to review medications and laboratory values and transmit any questions to the practice. An advanced HF nurse was hired for this clinical study who was dedicated to reviewing HF patient information. She was responsible for communicating with the patients through the Web site. The study nurse talked to the patients in the Internet and usual care groups by telephone when status was in doubt or when instructions were complicated enough that verification of understanding was needed. The information sent to the patient was intended to adjust the patient's general health status to maintain a stable HF state. The clinical team was

Kashem A, 2008

	experienced in providing instructions to the patient by telephone, and the same care protocols and clinical experience were used for managing patients using information transmitted via the Internet.
Outcomes	hospital admissions, emergency department visits
Follow-up length	12 months
Notes	

Mortara A, 2009

Participants	461 heart failure patients with NYHA class II-IV and LVEF ≤ 40%.
Mean age	60 years
Male percentage	85%
Countries	UK, Poland, Italy
Interventions	Patients allocated to home telemonitoring were further randomised into 3 groups. The first group (strategy 1) received monthly supportive telephone contacts from a study nurse to check on their clinical status. The second group (strategy 2) received the same telephone support, but also transmitted their vital signs and other data including details of changes in weight, BP and symptoms weekly by telephone. These patients also performed monthly 24h cardiorespiratory recordings which were not made available to the clinical team. The third group (strategy 3) carried out the same measurements as strategy 2 patients, but the monthly 24h cardiorespiratory recordings were made available for clinical management. Usual care was only described as usual outpatient care.
Outcomes	Mortality and hospitalisation due to HF, all-cause mortality, all-cause hospitalisation, bed-days occupancy (due to cardiovascular cause).
Follow-up length	11.6 months
Notes	

Soran O Z, 2008

Participants	315 patients with HF diagnosis secondary to systolic dysfunction (LVEF ≤ 40%).
Mean age	76 years
Male percentage	35%

Soran O Z, 2008

Country	USA
Interventions	Patients randomised to the Heart Failure Monitoring System (HFMS) cohort received a disease management program using telecommunication equipment including an electronic scale and individualised symptom response system linked to a database staffed by nurses. Patients weighed themselves and answered questions related to their heart failure. Patients were contacted if any changes were observed in symptoms or weight. Patients allocated to standard heart failure care (SC) received enhanced patient education, education to clinicians and follow-up. They were provided with a digital home scale to weigh themselves daily and educational materials related to worsening of HF and were asked to record heart failure symptoms. All patients were telephoned 30 days and 3 months post-randomisation for blinded clinical data collection (vital signs, hospital visits, quality of life questionnaires).
Outcomes	Treatment failure (cardiovascular mortality or re-hospitalisation for HF within 6 months), length of hospital stay, 6-month all-cause hospitalisation, 6-month heart failure hospitalisation, number of emergency room visits, Medicare expenditure, total patient costs, quality of life.
Follow-up length	Six months
Notes	Number of patients hospitalised calculated from reported % with any hospital admission.

Tibaldi V, 2009

Participants	101 heart failure patients with NYHA class III-IV
Mean age	81 years
Male percentage	51%
Country	Italy
Interventions	The inpatient control group received routine hospital care. Protocols for prevention of nosocomial infections, bed sores, and immobilization are routinely adopted for frail elderly inpatients. The intervention group included the patients treated at home by the Geriatric Home Hospitalization Service (GHHS). It provides substitutive hospital-at-home care in a clinical unit model and has been in operation for more than 20 years. The team, equipped with 7 cars, is multidisciplinary and consists of

Tibaldi V, 2009

	4 geriatricians, 13 nurses, 3 physiotherapists, 1 social worker, and 1 counselor. The main feature of the GHHS is that physicians and nurses work together as a team, with daily meetings to discuss the needs of each patient and to organize individualized medical care plans. The team operates 7 days a week and on average cares for 25 patients per day and 450 patients per year. The most common diseases treated at home are cardiopulmonary, cerebrovascular, metabolic, and neoplastic diseases. The GHHS can be activated by a direct request of the general physician of the patient as an alternative to traditional hospital care or by a request from hospital ward physicians to allow early and protected discharge from the hospital. Treatments included physician and nurse visits, standard blood tests, pulse oximetry, spirometry, electrocardiography, echocardiography, internistic echography and Doppler ultrasonography, ambulatory electrocardiography and arterial blood pressure monitoring, oral and intravenous medication administration (such as antimicrobials and cytotoxic drugs), oxygen therapy, blood products transfusion, central venous access, surgical treatment of pressure sores, physical therapy, occupational therapy, and counseling.
Outcomes	Mortality, hospitalization
Follow-up length	6 months
Notes	

Woodend A K, 2008

Participants	121 patients with symptomatic heart failure (NYHA Class II or greater).
Mean age	68 years
Male percentage	74%
Country	Canada
Interventions	Daily transmission of weight and periodic transmission of ECG and BP. Weekly video conferences by tele-home care nurse. Video conferences more frequent in first few weeks and tapered over the 3 months. Usual care was not described.
Outcomes	Mortality, rehospitalisation, quality of life, emergency department visits, patient satisfaction.
Follow-up length	12 months
Notes	Mortality data included in previous systematic review and

2.3 Disease Management Program versus Home-monitoring

A wide literature investigates effects of HM or DMP on clinical outcomes of patients suffering from CHF[5-14]. In almost the totality of study, those models have been compared to ambulatory follow up, which is considered the usual care (benchmark) as it is recommended by international guidelines[20]. Nonetheless, there is not wide literature that compares directly costs and outcomes of HM and DMP[15-17]. Nonetheless, this comparison is needed since many National Health Services, in particular the Italian one[18], are starting considering Home-monitoring to overcome usual care, but although there is strong evidence that HM overcomes DMP, there is a preliminary study proving that HM are more costly (up to five times) than DMP[19].

2.3.1 Meta-analysis for comparison of the efficacy

For each outcome, two independent meta-analysis were performed in order to compare DMP with UC and HM with UC, respectively. In both meta-analyses, continuous outcomes were expressed by Mean Differences, with the relative 95% Confidence Interval; binary outcomes were expressed by Relative Risks, with the relative 95% Confidence Interval. The heterogeneity was assessed by using the Chi-square Test and a p-value less than 0.05 was considered statistically significant. When the heterogeneity test was statistically significant, the Random Effect Model was adopted, otherwise the fixed-effects models[23].

The software Meta-Analyst was used to process data[24]; the results were represented by forest plots, while funnel plots were examined because of the potential of publication bias. Finally, effect size of DMP and HM was

assessed using network meta-analysis[25]. To assess the variation between studies, I used the statistic Chi-squared as the difference of the overall heterogeneity and the measures of the heterogeneity in the two primaries meta-analyses[26].

2.3.1.1 Network meta-analysis

The Network Meta-analysis (NM) is a method for indirect comparison of two or more treatments, when the available evidence consists of a network of multiple RCTs involving treatment compared directly or indirectly or both[27]. While traditional meta-analysis provides a direct comparison using studies comparing the same intervention with the same comparator (for instance, placebo or gold standard), NM enables multiple pair-wise comparison across several interventions and provides estimates of relative treatment effect on multiple comparative comparisons.

NM could be applied to network of RCTs of different complexities. In the current thesis, it was applied to the simplest network of RCTs, in which g studies compared the treatment A with the control C and h studies compared the treatment B with the control C, and the NM enables the indirect comparison between A and B. In the case study, Home-monitoring and Disease Management Programs represents the treatments A and B, respectively, while the Usual Care represents the control C. In this case (in which the network does not consist of loop), two tradition meta-analyses were performed to directly compare treatment A versus C and treatment B versus C, and then, the results were pooled according to the methodology of NM proposed by Bucher[26] and described also by [28].

2.3.2 Research strategy

From previously published meta-analysis about DMP and HM for patients affected by heart failure [5-14], the research was restricted to randomized controlled trials (RCTs) published in English peer-reviewed literature; no

restriction on publications dates was applied. An electronic search in the MedLine's and the Cochrane's Databases was performed considering the following keywords, in combination with the boolean operators And/Or:

- heart failure;
- disease management program;
- usual care;
- home-monitoring;
- telemonitoring;
- structured telephone service.

The aim was to find RCTs comparing Chronic Heart Failure management delivered via disease management programs or via home-monitoring with usual post-discharge care in patients with CHF living within community.

A study was excluded if:

- the follow-up was shorter than 6 months or longer than 18 months;
- its aim was not coherent with the current study (for instance, it make a comparison between DMP and HM or did not provide outcome of interest in an extractable form);
- it reported redundant or incomplete data (for instance, multiple publication of the same RCT);
- its full-text was not in English language;
- it reported data of a three arms randomized controlled trials.

For the purpose of the current research, three strategies of care were idenfied: usual care, disease management program (without the support of technology), technology-assisted home monitoring program.

For the purpose of this study, the following definition was adopted:

- Usual Care, further referred as UC, consists of standard post-discharge care without intensified attendance at cardiology clinics or clinic-based CHF disease management program or home visiting[5];

- Disease Management Program (without the support of technology), further referred as DMP, consists of coordinated and multidisciplinary healthcare intervention and communication6. DMP may include a telephone monitoring approach including regularly scheduled structured telephone contacts between patients and health care providers (with or without home visits) and reporting of symptoms and/or physiological data[10];
- Technology-assisted Home Monitoring program, further referred as HM, is the model in which the DMP is integrated by remote monitoring of signs, symptoms, physiological parameters, and biomedical signals. For that reason, it includes a strong adoption of information and communication technology (ICT) [10].

All the full-text were independently analyzed by two investigators (PM - the author of the thesis and Dr Leandro Pecchia LP – the co-supervisor of the thesis) in order to classify the strategies proposed by the RCT as UC, DMP or HM and independently extracted the data from the included studies. A third reviewed (Prof. Marcello Bracale MB – the supervisor of the thesis) adjudicated in the instance of disagreement between the first two investigators and checked all the extracted data.

84 RCTs matched the research strategy: 18 [29, 30] of them were not fully coherent with the aim of this Study; 10 papers [16] reported redundant or insufficient data; 9 papers [31] were excluded as they did not report data about of follow-up durations between 6 and 18 month; 3 [32] were not in English language; 2 were three arms RCTs which provided data about UC, DMP and TM. Thus, 42 studies were included, of which 31 RCTs compared DMP and UC and 11 compared HM and UC. Table 3 reports the excluded studies and the relative reason of exclusion.

Table 3: List of excluded studies and relative motivation

First Author, Year	Motivation for exclusion
Aiken LS, 2006 [29]	not coherent with the objective

First Author, Year	Motivation for exclusion
Albanese MC, 2001 [32]	paper not in English language
Barth V, 2001 [31]	duration of follow-up not within 6-18 month
Beckers PJ, 2010 [30]	not coherent with the objective
Benatar D, 2003 [16]	redundant or incomplete data
Capomolla S, 2002 [33]	not coherent with the objective
Capomolla S, 2004 [34]	redundant or incomplete data
Carrington MJ, 2010 [35]	not coherent with the objective
Chang BH, 2005 [36]	not coherent with the objective
Clark R A, 2007 [37]	not coherent with the objective
Cleland J G, 2005 [15]	RCTs in three arms
Evans, RS, 2010 [38]	not coherent with the objective
Fabbri G, 2007 [39]	paper not in English language
Fulmer TT, 1999 [17]	RCTs in three arms
Grancelli H, 2003 [40]	redundant or incomplete data
Harrison M B, 2002 [41]	duration of follow-up not within 6-18 month
Jenkins R L, 2001 [42]	not coherent with the objective
Jerant A F, 2001 [43]	duration of follow-up not within 6-18 month
Kielblock B, 2007 [44]	paper not in English language
Koehler F, 2010 [45]	not coherent with the objective
Laramee A S, 2003 [46]	duration of follow-up not within 6-18 month
McDonald K, 2001 [47]	duration of follow-up not within 6-18 month
McDonald K, 2002 [48]	duration of follow-up not within 6-18 month
Murray, 2004 [49]	not coherent with the objective
Nahm E S, 2008 [50]	not coherent with the objective
Naylor M, 1999 [51]	redundant or incomplete data
Naylor M, 1994 [52]	duration of follow-up not within 6-18 month
Naylor M, 1999 [53]	redundant or incomplete data
Peters-Klimm, 2008 [54]	not coherent with the objective
Prescott E, 2009 [55]	redundant or incomplete data
Ramachandran,2007 [56]	not coherent with the objective
Rich M W, 1995 [57]	duration of follow-up not within 6-18 month
Schwarz K A, 2008 [58]	duration of follow-up not within 6-18 month
Smeulders ES, 2009 [59]	not coherent with the objective

First Author, Year	Motivation for exclusion
Stewart S, 1998 [60]	redundant or incomplete data
Stewart S, 1999 [61]	redundant or incomplete data
Stewart S, 1999 [62]	redundant or incomplete data
Varma S, 1999 [63]	not coherent with the objective
Villani A, 2007 [64]	not coherent with the objective
Wakefield B, 2008 [65]	redundant or incomplete data
Whitten, 2007 [66]	not coherent with the objective
Zugck C, 2005 [67]	not coherent with the objective

Table 4 reports the list of included studies.

Table 4: list of included studies

First Author, Year	Comparison
Antonicelli R, 2008 [68]	RCT comparing HM and UC
Atienza F, 2004 [69]	RCT comparing DMP and UC
Balk A H, 2008 [70]	RCT comparing HM and UC
Blue L, 2001 [71]	RCT comparing DMP and UC
Bourge R C, 2008 [72]	RCT comparing HM and UC
Bouvy M L,2003 [73]	RCT comparing DMP and UC
Cline C M, 1998 [74]	RCT comparing DMP and UC
de Lusignan S 2001 [75]	RCT comparing HM and UC
DeBusk R F, 2004 [76]	RCT comparing DMP and UC
DeWalt D A 2006 [77]	RCT comparing DMP and UC
Doughty R N, 2002 [78]	RCT comparing DMP and UC
Dunagan W C, 2005 [79]	RCT comparing DMP and UC
Ekman I, 1998 [80]	RCT comparing DMP and UC
Galbreath A D, 2004 [81]	RCT comparing DMP and UC
Gattis W A, 1999 [82]	RCT comparing DMP and UC
Giordano A, 2009 [83]	RCT comparing HM and UC

First Author, Year	Comparison
Goldberg L R, 2003 [84]	RCT comparing HM and UC
Hughes S L, 2000 [85]	RCT comparing DMP and UC
Jaarsma T, 1999 [86]	RCT comparing DMP and UC
Kashem A, 2008 [87]	RCT comparing HM and UC
Kasper E K, 2002 [88]	RCT comparing DMP and UC
Krumholz H M, 2002 [89]	RCT comparing DMP and UC
Mejhert M, 2004 [90]	RCT comparing DMP and UC
Mortara A, 2009 [91]	RCT comparing HM and UC
Naylor M D, 2004 [92]	RCT comparing DMP and UC
Peters-Klimm F, 2010 [93]	RCT comparing DMP and UC
Philbin E F, 2000 [94]	RCT comparing DMP and UC
Rainville E C 1999 [95]	RCT comparing DMP and UC
Rich M W, 1993 [96]	RCT comparing DMP and UC
Riegel B, 2002 [97]	RCT comparing DMP and UC
Riegel B, 2006 [98]	RCT comparing DMP and UC
Sisk J E, 2006 [99]	RCT comparing DMP and UC
Soran O Z, 2008 [100]	RCT comparing HM and UC
Stewart S 2002 [101]	RCT comparing DMP and UC
Stromberg A, 2003 [102]	RCT comparing DMP and UC
Thompson DR, 2005 [103]	RCT comparing DMP and UC
Tibaldi V, 2009 [104]	RCT comparing HM and UC
Tsuyuki R T, 2004 [105]	RCT comparing DMP and UC
Wakefield B J,2008 [106]	RCT comparing DMP and UC
Weinberger M, 1996 [107]	RCT comparing DMP and UC
Woodend A K, 2008 [108]	RCT comparing HM and UC
Young W, 2003 [109]	RCT comparing DMP and UC

2.3.3 Identified Outcome

From the results of previously published meta-analysis[3, 5-14] and of our research, the following outcomes were selected:

1. all-cause cause mortality;
2. HF-related mortality;
3. number of patients readmitted for all causes;
4. number of patients readmitted for HF-related causes;
5. bed-days of care for all causes;
6. bed-days of care for HF-related causes.

2.3.4 Results of the comparison

All cause mortality data were available from 24 studies comparing DMP with UC (Figure 1) and 7 studies comparing HM with UC (Figure 2). I found that DMP and HM were related to a lower number of death for all causes compared with the UC (RR=0.86, 95%IC=0.73, 1.01; RR=0.62, 95% IC=0.45, 0.84; respectively) but the effect size was significant only for HM.

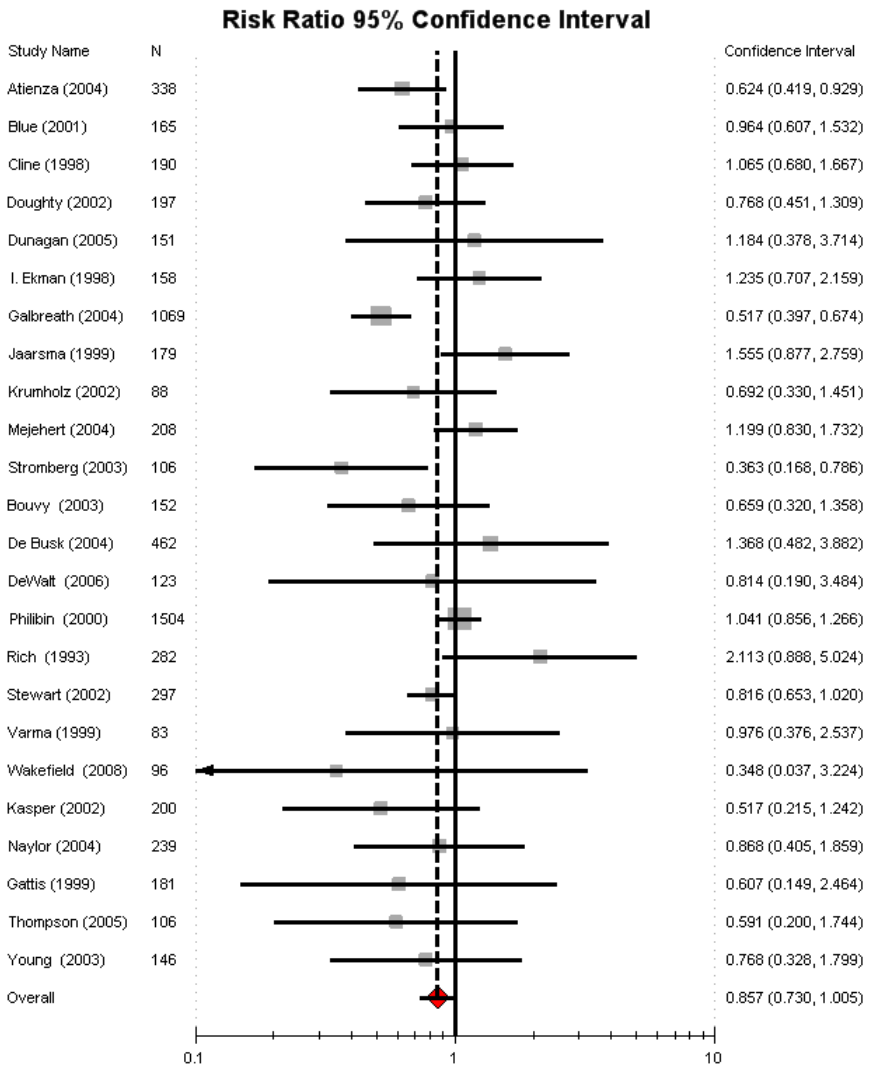

Figure 1: impact of Disease Management Programs of patients suffering from Chronic Heart Failure on risk of all-cause mortality compared with Usual Care

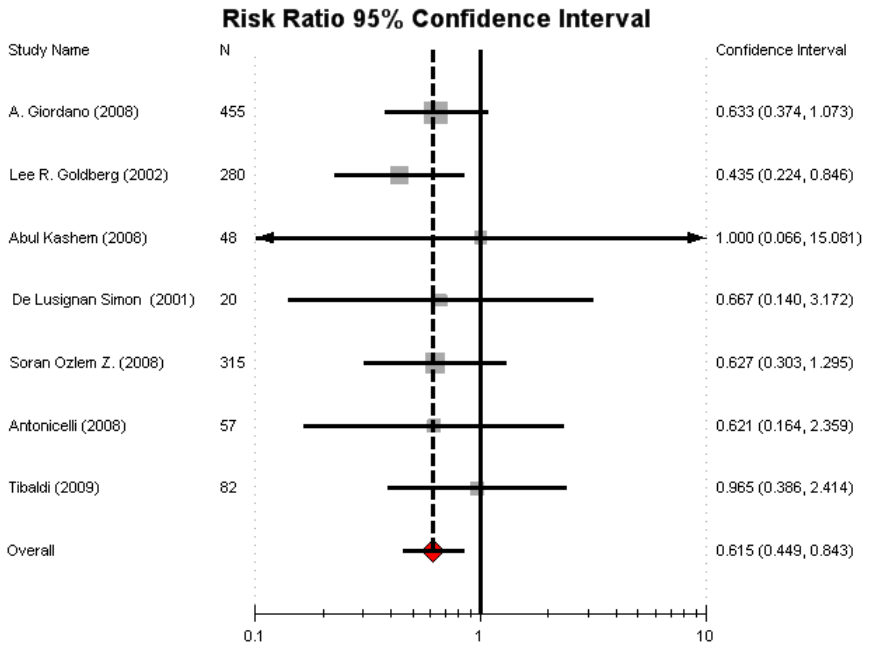

Figure 2: impact of Home-monitoring of patients suffering from Chronic Heart Failure on risk of all-cause mortality compared with Usual Care

HF-related mortality data were available from 5 studies comparing DMP with UC (Figure 3) and 2 studies comparing HM with UC (Figure 4). Both DMP and HM were related to a reduction of HF related mortality (RR=0.67, 95%IC=0.43, 1.04; RR=0.60, 95%IC=0.37, 0.98; respectively), but the effect size was significantly only for HM.

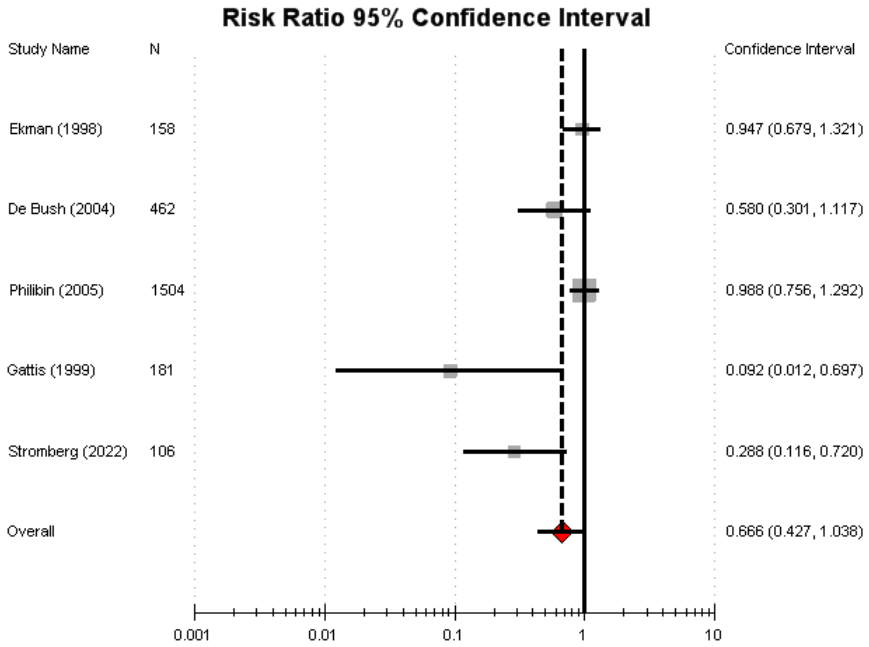

Figure 3: impact of Disease Management Programs of patients suffering from Chronic Heart Failure on risk of HF-related mortality compared with Usual Care

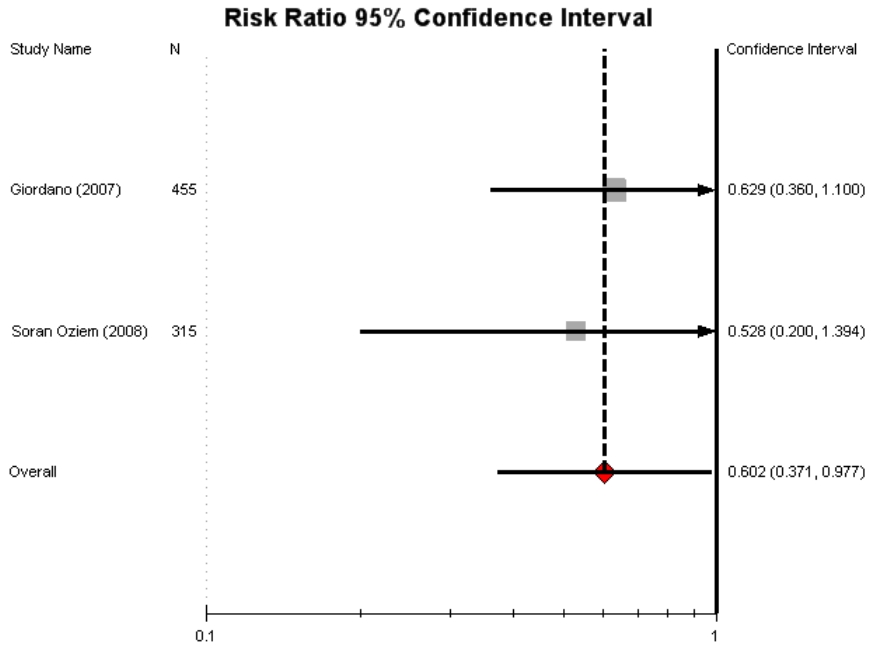

Figure 4: impact of Home-monitoring of patients suffering from Chronic Heart Failure on risk of HF-related mortality compared with Usual Care

Data regarding the number of patients readmitted for all causes were available from 15 studies comparing DMP with UC (Figure 5) and from 3 studies comparing HM with UC (Figure 6). Comparing DMP or HM to UC, I did not find a statistical statistically significant differences for this outcome (RR=0.96, 95%IC=0.87, 1.07; RR=0.80, 95%IC=0.51, 1.25; respectively).

HF-related hospitalization rate data were available from 15 studies comparing DMP with UC (Figure 7) and from 4 studies comparing HM with UC (Figure 8).

Both DMP and HM was related to a significantly lower number of patients readmitted for HF (RR=0.70, 95%IC=0.55, 0.90; RR=0.71, 95% IC=0.53, 0.97; respectively)

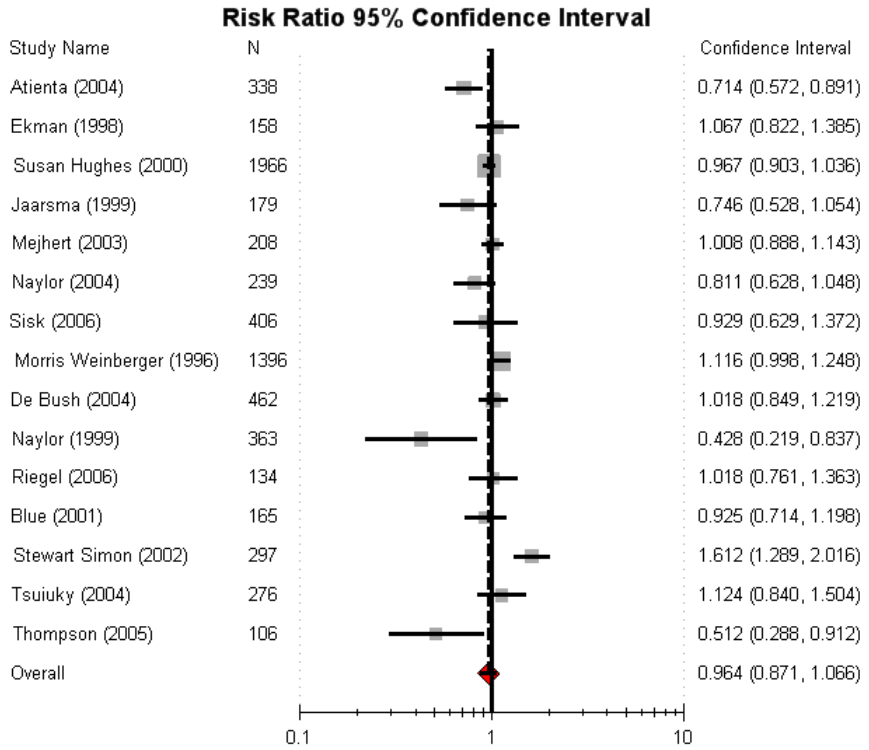

Figure 5: impact of Disease Management Programs of patients suffering from Chronic Heart Failure on all-cause readmission rate compared with Usual Care

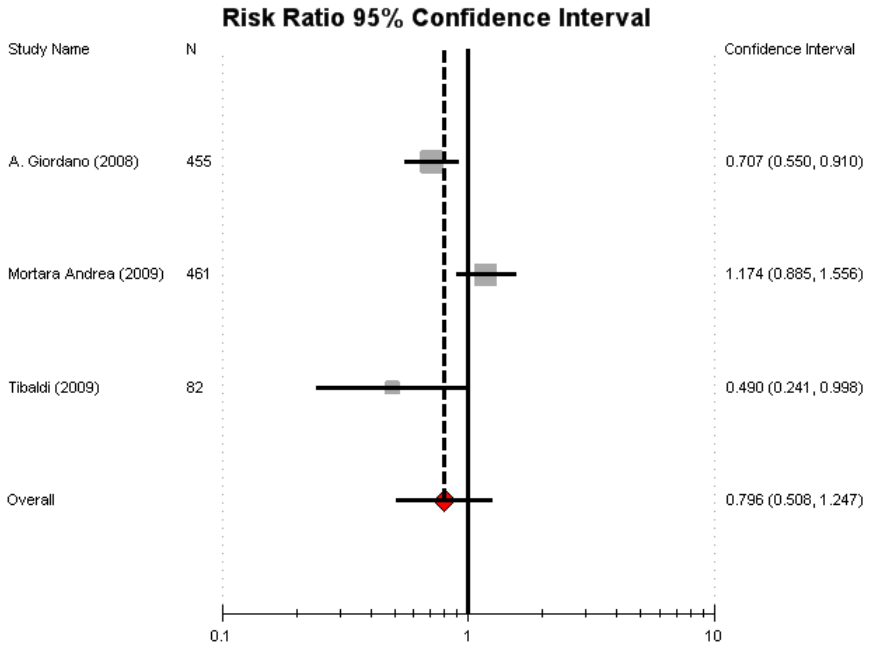

Figure 6: impact of Home-monitoring of patients suffering from Chronic Heart Failure on all-cause readmission rate compared with Usual Care

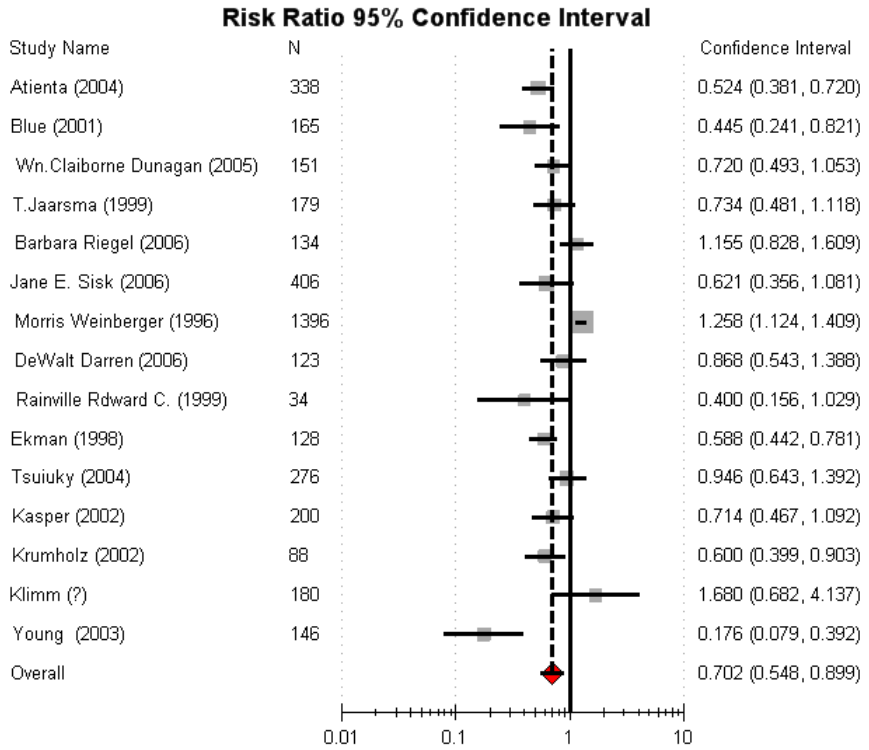

Figure 7: impact of Disease Management Programs of patients suffering from Chronic Heart Failure on HF-related readmission rate compared with Usual Care

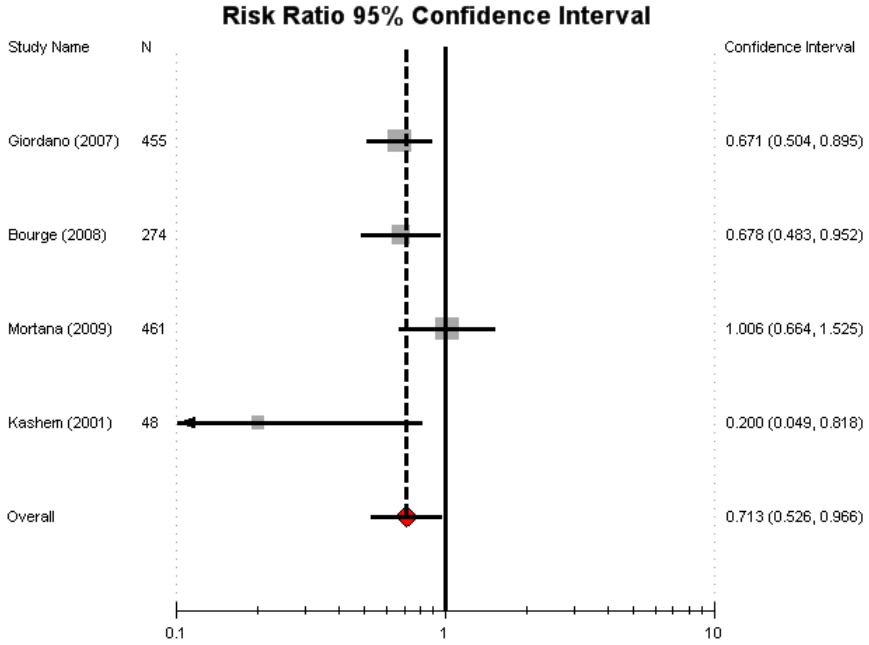

Figure 8: impact of Home-monitoring of patients suffering from Chronic Heart Failure on HF-related readmission rate compared with Usual Care

All cause bed days of care data were available from 15 studies comparing DMP with UC (Figure 9) and from 4 studies comparing HM with UC (Figure 10). Comparing DMP or HM to UC, I did not find a statistical

statistically significant differences for this outcome (MD=-1.09, 95%IC=-2.70, 0.53; MD=-0.12, 95%IC= -1.63, 1.40; respectively).

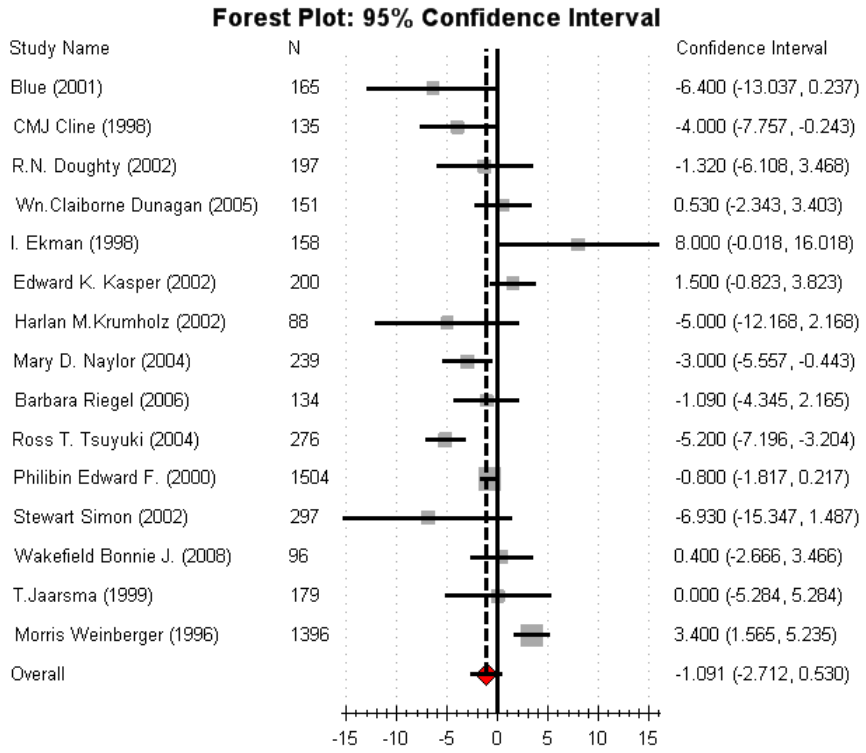

Figure 9: impact of Disease Management Programs of patients suffering from Chronic Heart Failure on numbers of all-cause bed days of care compared with Usual Care

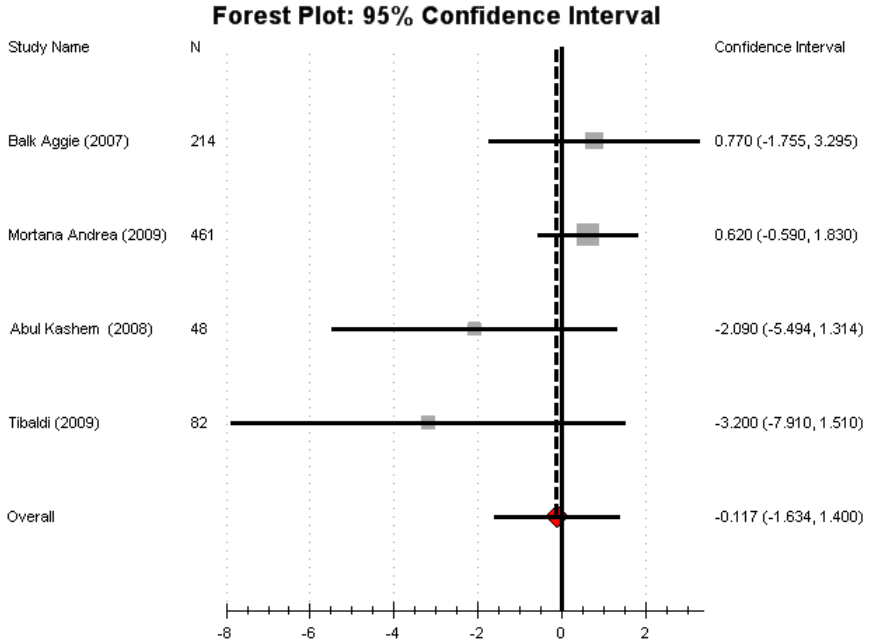

Figure 10: impact of Home-monitoring of patients suffering from Chronic Heart Failure on numbers of all-cause bed days of care compared with Usual Care

HF-related bed days of care data were available from 6 studies comparing DMP with UC (Figure 11) and 3 studies comparing HM with UC (Figure 12). Comparing DMP or HM to UC, I did not find a statistical statistically significant differences for this outcome (MD: -1.03, 95% IC: -3.90, 1.85; MD=-0.35, 95%IC=-2.02,1.32; respectively).

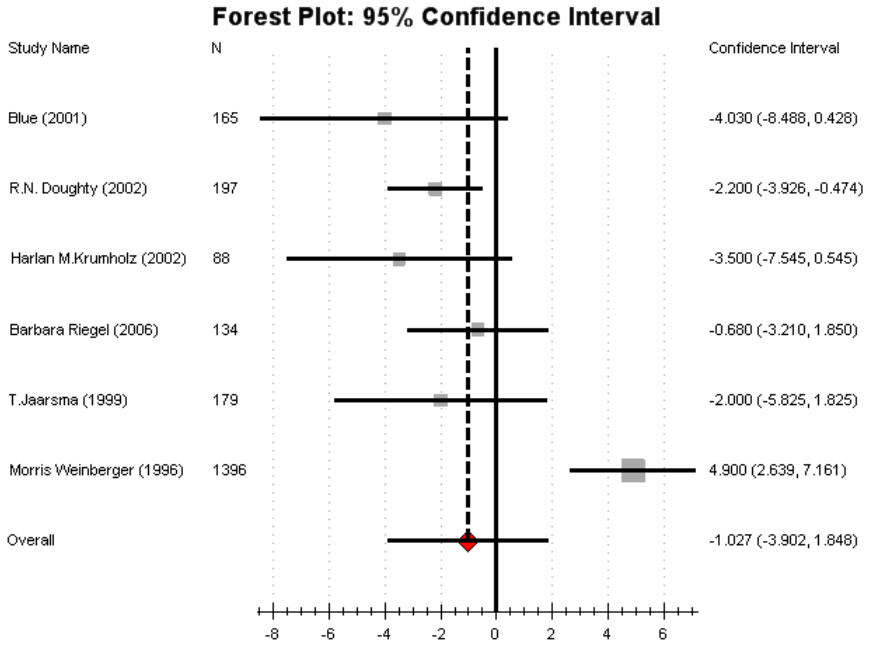

Figure 11: impact of Disease Management Programs of patients suffering from Chronic Heart Failure on numbers of HF-related bed days of care compared with Usual Care

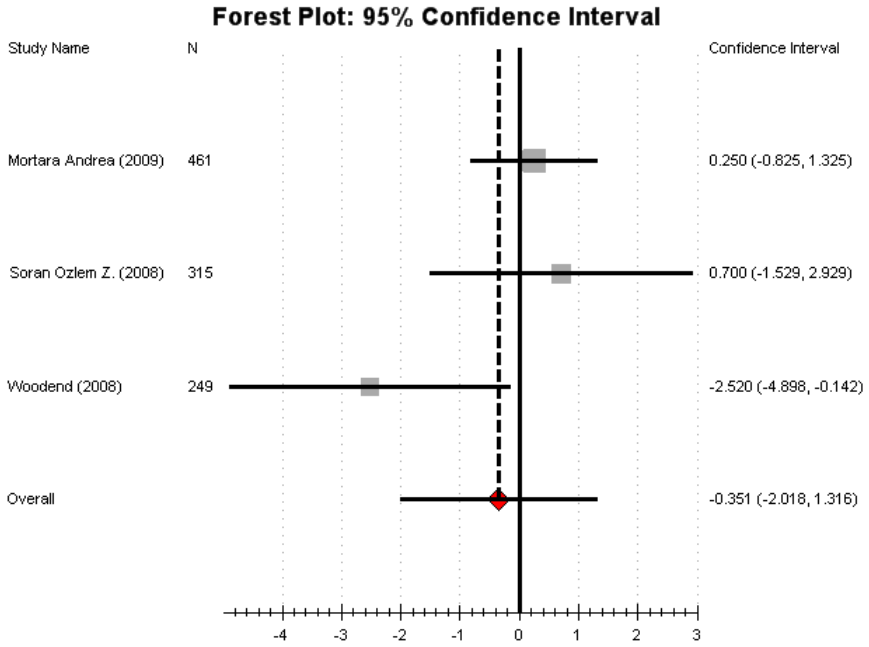

Figure 12: impact of Home-monitoring of patients suffering from Chronic Heart Failure on numbers of HF-related bed days of care compared with Usual Care

Table 5 summarizes the results of the direct comparisons between DMP and UC, and HM and UC for the binary outcomes and shows the results of the network meta-analysis for the indirect comparison between DMP and UC (see last column). No statistically significant differences between DMP and HM for the binary outcomes was found.

Table 5: Comparison of Relative Risk (RR) between Disesase Management Programs (DMP) and Usual Care (UC), Home-Monitoring (HM) and Usual Care, and Home-Monitoring and Disease Management Programs for each selected binary outcome

Binary outcomes	DMP vs UC RR (95%IC; p)	HM vs UC RR (95%IC; p)	HM vs DMP RR (95%IC; p)
All-cause mortality	0.86 (0.73, 1.01; p>0.05)	0.62 (0.45, 0.84; p<0.05)	0.72 (0.51, 1.01; p>0.05)
HF-related mortality	0.67 (0.43, 1.04; p>0.05)	0.60 (0.37, 0.98; p<0.05)	0.90 (0.46, 1.52; p>0.05)
# of patients readmitted for all causes	0.96 (0.87, 1.07; p>0.05)	0.80 (0.51, 1.25; p>0.05)	0.83 (0.57, 1.22; p>0.05)
# of patients readmitted for HF	0.70 (0.55, 0.90; p<0.05)	0.71 (0.53, 0.97; p<0.05)	0.83 (0.57, 1.22; p>0.05)

Table 6 summarizes the results of the direct comparisons between DMP and UC, and HM and UC for the continuous outcomes and shows the results of the network meta-analysis for the indirect comparison between DMP and UC (see last column). No statistically significant differences between DMP and HM for the continuous outcomes was found.

Table 6: Comparison of Mean Difference (MD) between Disease Management Programs (DMP) and Usual Care (UC), Home-Monitoring (HM) and Usual Care, and Home-Monitoring and Disease Management *Programs for each selected binary outcome

Continuous Outcomes	DMP vs UC MD (95%IC; p)	HM vs UC MD (95%IC; p)	HM vs DMP MD (95%IC; p)
Bed days of care for all causes	-1.09 (-2.71, 0.53; p>0.05)	-0.12 (-1.63, 1.40; p>0.05)	0.97 (-0.70, 2.61; p>0.05)
Bed days of care for HF	-1.03 (-3.90, 1.85; p>0.05)	-0.35 (-2.02, 1.32; p>0.05)	0.68 (-2.0, 3.36; p>0.05)

2.4 Discussion and conclusion

From the results presented in this chapter, it emerged that HM significantly reduced mortality, either for all-causes either for HF-related causes, and number of patients readmitted for HF-related causes, while DMP significantly reduced number of patients readmitted for HF-related causes.

These results confirms those of previously published meta-analyses about "disease management programs"[9, 14], "structured telephone support" and "Telemonitoring"[5, 8, 10, 12, 13] in showing the effectiveness of these strategy compared to UC in order improving the main clinical outcome. For instance, the results about all-cause mortality are in line with the findings of the recent meta-analyses by Inglis[5] comparing Structured telephone support programs with UC and Telemonitoring programmes with UC. I underlined that almost all "structured telephone support" programs of these reviews were classified as DMP for the purpose of the current study, while almost all "Telemonitoring" ones were included among the HM strategy.

Moreover, the current study compared HM to DMP using a Network Meta-analysis, which enables an indirect comparison between the two models of care in spite of the lack of a sufficient number of RCTs which would enables a direct comparison. The results of the indirect comparison showed that there is not significant evidence that HM overcomes DMP. Nonetheless, the indications of effect size reported in Table 5 and in Table 6 seems to confirm the conclusions of the few available RCTs[17], which stated that HM improved DMP even if the difference was not always statistically significant. In particular, Benatar[16] showed that readmission rate at 6 months was significantly lower in the TM compared with the DMP group. Results by Cleland [15] showed that all-cause mortality was reduced by both strategies compared with UC but no significant differences were observed between HM and DMP in the primary or secondary outcomes

selected. Similarly, no significantly statistical difference was reported by Fulmer [17].

The main limit of the results shown in this chapter is the fewer number of RCTs considering TM than those considering DMP. Since, given the weight of evidence, further RCTs of “structured telephone support” and “Telemonitoring” in comparison of usual care were not recommend, I suggest that RCTs comparing strategy of care with different intervention intensity should be performed in order to enable a direct comparison.

In conclusion, an indirect comparison of Home Monitoring and Disease Management Programs was performed by a network meta-analysis of randomized controlled trial comparing HM or DMP with usual care. Both strategies of care improved significantly some clinical outcomes compared to usual care, for instance the number of patients readmitted for Heart Failure. The indirect comparison showed that there was no significant difference in the effect size for the selected outcomes.

3. Enhancement of Telemedicine service with Data-Mining: CHF detection and assessment

3.1 Description of the telemedicine plaftorm developed for the Project Remote Health Monitoring

In this chapter, I present the system developed for Remote Health Monitoring (RHM) of patients suffering from Heart Failure, which includes advanced functionalities of data-mining for continuous patient monitoring. The clinical goal was the early detection of any worsening in patient's condition, with automatic "HF severity assessment" using data-mining, assuming that during worsening, patients will gradually show characteristic of a more severe HF. The system was developed in the last three years.

First, I described briefly the whole platform developed for the Project Remote Health Monitoring I contribute to design and develop, then I present the methods employed and to present the preliminary results of the data mining for HF detection and severity assessment. The results described were obtained testing the system with biomedical signals from public databases, in order to allow other scientists to reproduce them, and because results clinical trials involving local patients were not available at the time of writing the current chapter.

3.2 Description of the platform

The system designing followed the so-called "Three Tier architecture". Functionally, the platform consisted of three parts, called "Areas": "Client Area" (CA) acting as presentation tier, "Server Area" (SA) as business tier and data tier and the "Web Service Area" (WSA) as pure business tier level. The CA aimed to present and to collect data using devices, which differed according to the users and the scenarios. The SA aimed to manage, store and retrieve data and included the Electronic Patient Record (EPR) and an Interactive Voice Response (IVR)[110], which acted as audio user interface. The WSA was used for raw data processing, signal analysis and data mining. IVR allowed users less skilled with web technologies to insert

daily ECG records and physiological parameters (pressure, weight and temperature). The IVR, after a login, gave the user all the instructions and recommendations to send data, repeating, when possible, the entered values and asking for further confirmation.

The devices tested and integrated in the system, varied according to the scenario, going from user-friendly ones for self-recording of signals/signs to professional multi-parametric monitors, recording ECG, blood pressure (BP), hart rate (HR), SpO2, temperature (T), Galvanic Skin Response (GSR), skin near-body temperature (ST), respiratory frequency (RF), Activity (A) and Posture (P).

According to the scenario, the software/hardware and the communication line to allow data sending also varied. The RHM platform was tested in three different scenarios: home care, medical ambulatory and hospital.

3.3 Data-mining application

The platform supported a strategy of automatic classifications consisting of two steps: “HF detection” and “HF severity assessment”. The former was used in the platform to pre-screen patients before they underwent the latter. The whole classification aimed to early detection of any worsening, assuming that during worsening, patients will gradually show characteristic of a more severe HF. Both classifiers were based on the Classification and Regression Tree method. Although the system collected several data, at the moment only features obtained from ECG records were adopted for the data-mining functionalities.

3.3.1 Classification and Regression Tree

The CART is an algorithm to develop classification trees from the top down using a process known as binary recursive partitioning. It consists of two steps: tree growing and tree pruning.

The former step is an iterative process in which the data are split repeatedly into groups, called as child nodes. The split is based on a single variable and can be expressed by a if-then rule: "if selected-feature-value is higher than cut-off-value, then go into child node 2, else go into child node 1". Among possible splits, those which generate the "purer" child nodes, where the purest node is the one containing elements of only one class. Among different functions that have been proposed for the measure of the impurity of each node "t"[111], I adopted the Gini index criterion, which, for binary classification, can be computed as follows:

$$Gini\ index(t) = 1 - \left(\frac{n_i}{n}\right)^2 - \left(\frac{n_j}{n}\right)^2 \qquad (1)$$

where "t" is the considered node, "i" and "j" are the two class labels, "n_i" and "n_j" are the number of subject present at the node belonging to the class "i" or "j", respectively, and n is the number of subject present at the node. The tree growing stops when no further split is possible and the outcome of this step is referred to as the Large-Tree (LT).

In the latter step, the tree is pruned, according to a minimal cost-complexity function, which relies on the size of the tree (number of nodes) and the misclassification probability (MP). I estimated the MP performing a 10-fold-crossvalidation. This technique consists in developing 10 trees as following: (1) dividing randomly the dataset into 10 subsamples; (2) excluding a subsample (testing subset) in turn; (3) developing each tree with the remaining 9 subsamples (training subset); (4) testing each tree with the excluded subsample (which is used as an independent testing dataset), computing the ratio of misclassified cases (mp_i). The MP of the tree is the average over the 10 ratios of misclassified cases mp_i. I decided to divide the data-set by subjects and not by records, as two records of the same subject could not be considered as independent.

Further details on CART growing and pruning can be found in Breiman [111].

3.3.2 Data

The results described in this chapter were obtained testing the system with biomedical signals from public databases, in order to allow other scientists to reproduce them, and because results from clinical trials involving local patients were not available at the time of writing the current chapter.

The dataset consisted into 116 nominal 24-hour records, from 72 normal subjects and 44 suffering from CHF. The overall dataset consisted of 54 men, 43 women and 19 unknown-gender subjects, aged 20 to 79 (55±14 years). The normal subjects were 35 men and 37 women, aged 20 to 76 (55±16 years). The CHF subjects were 19 men, 6 women and 19 unknown-gender subjects, aged 22 to 79 (56±11 years).

The data for normal subjects were retrieved from the Normal Sinus Rhythm RR Interval Database [112] and from the MIT-BIH Normal Sinus Rhythm Database [112]. The former includes RR intervals extracted from 24-hour ECG recordings from 30 men and 24 women, aged 29 to 76 (61±12 years). The latter includes long-term ECG recordings from 5 men and 13 women, aged 20 to 50 (61±8 years). The data for the CHF group were retrieved from the Congestive Heart Failure RR Interval Database [112] and from the BIDMC Congestive Heart Failure Database [112]. The former includes RR intervals extracted from 24-hour ECG-Holter recordings of 8 men, 2 women, and 19 unknown-gender subjects, aged 34 to 79 (55±11 years). The latter database includes long-term ECG recordings from 11 men and 4 women, aged 22 to 71 (56±11 years), with severe congestive heart failure.

All the records are provided with beat annotations obtained by automated analysis with manual review and correction, with the exception of beat annotations from the BIDMC Congestive Heart Failure Database which

were not manually corrected. All the original ECG records were digitized at 128 samples per second, with the exception of the records from the BIDMC Congestive Heart Failure Database, which were sampled at 250 samples per second.

3.3.3 Long-term HRV analysis

Standard long-term HRV analysis was performed on nominal 24-hour recordings according to International Guidelines[113].

The series of normal to normal (NN) beat intervals were obtained from the beat annotation files of the selected four databases and the NN/RR ratio was computed as the fraction of total RR intervals classified as normal-to-normal (NN) intervals. This ratio has been used as a measure of data reliability, excluding records with a ratio less than a threshold. Thresholds of 80%[112] and 90%[114] were proposed. I chose a threshold of 85%, as it was a satisfactory trade-off between numbers of included subjects and quality of NN signals. Using this technique, 6 records were excluded (5 CHF and 1 normal) and the final dataset consisted of 110 subjects: 71 healthy people and 39 CHF patients.

All the computed basic time- and frequency-domain HRV measures were widely used in the literature[113, 115]. A number of standard statistical time-domain HRV measures are calculated: AVerage of all NN intervals (AVNN), Standard Deviation of all NN intervals (SDNN), Standard Deviation of the Averages of NN intervals in all 5-minute segments of a 24-hour recording (SDANN), mean of the Standard Deviations of NN intervals in all 5-minute segments of a 24-hour recording (SDNN IDX), square Root of the Mean of the Sum of the Squares of Differences between adjacent NN intervals (RMSSD), percentage of differences between adjacent NN intervals that are longer than 50 ms (pNN50). Moreover, percentage of differences between adjacent NN intervals that are longer than 12 ms (pNN12) was computed because Mietus [116] showed that

among pNNx measures pNN12 can provide the maximum separation between normal subjects and CHF patients.

The frequency-domain HRV measures rely on the estimation of power spectral density (PSD). Several methods were proposed in literature in order to estimate PSD of RR intervals [113, 115]. For this research, PSD were estimated by both by Welch's averaged modified periodogram[117] and by Lomb-Scamble periodogram[118]. For the Welch's periodgram, the NN interval was first interpolated with cubic spline interpolation at 4 Hz. The interpolated series was divided into overlapping segments of length 4000 points and each segment was Hanning windowed. The overlap was chosen to be 1200 points[114]. After PSD estimation, six standard frequency-domain HRV measures were calculated: total spectral power of all NN intervals up to 0.4 Hz (TOTPWR), between 0 and 0.003 Hz (ULF), between 0.003 and 0.04 Hz (VLF), between 0.04 and 0.15 Hz (LF), between 0.15 and 0.4 Hz (HF), ratio of low to high frequency power (LF/HF). Further in this chapter, I will refer Welch-based measures and the Lomb-Scamble-based ones by using the subscript W and LS, respectively. For instance, $TOTPWR_W$ refers to the estimation of TOTPWR computed by using Welch periodgram, while $TOTPWR_{LS}$ refers to the one obtained by Lomb-Scamble periodgram.

3.3.4 Heart Failure detection

The results of the data-mining methods adopted consisted into a decision tree like those proposed in Figure 13 and Figure 14. These trees enables the automatic detection of Heart Failure.

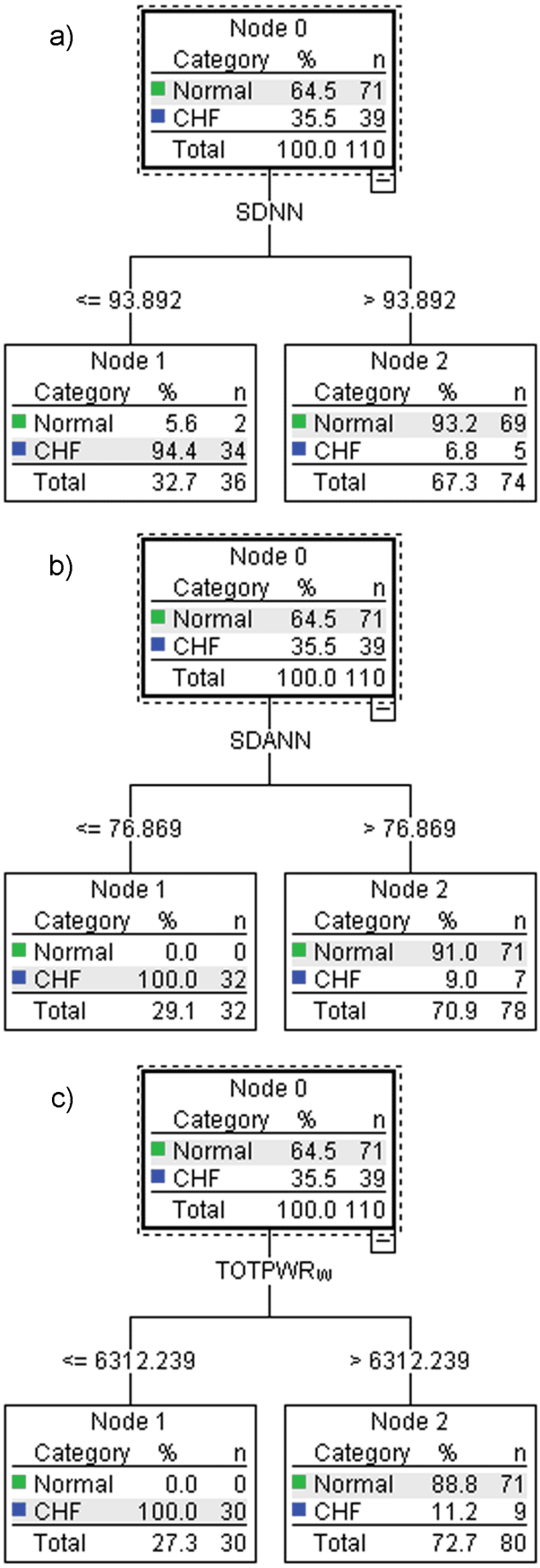

Figure 13: The final model tree for the following HRV features: a) SDNN, b) SDANN, c) $TOTPWR_W$

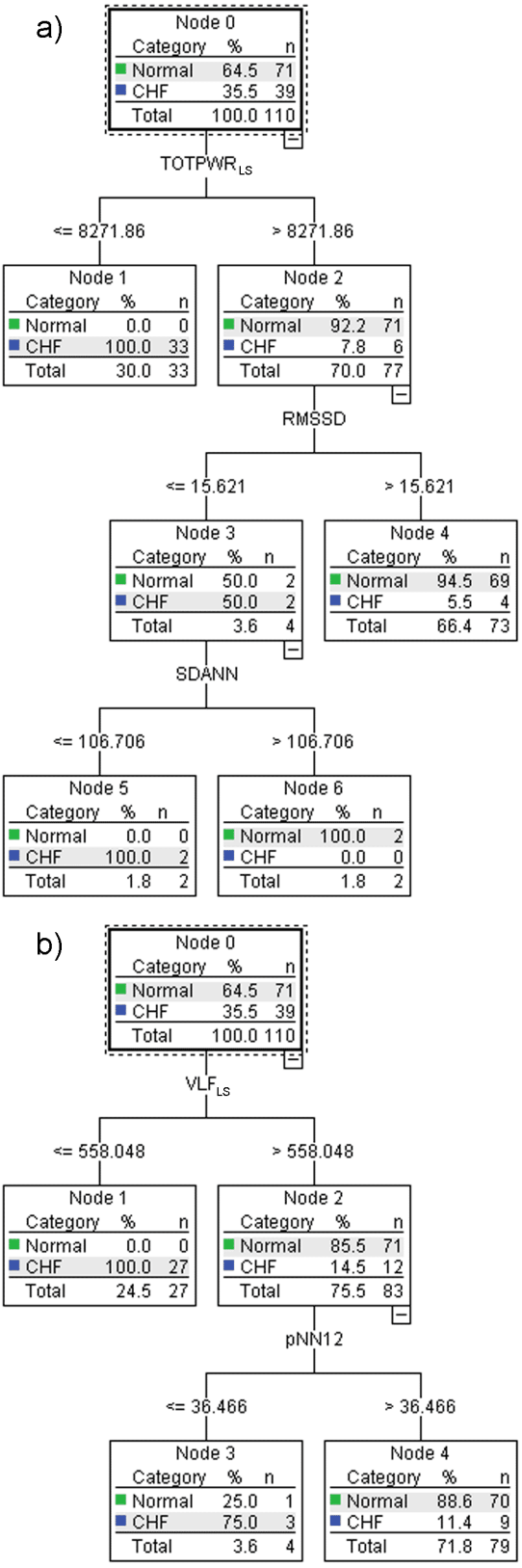

Figure 14: The final model tree for the following combinations of HRV features: a) $TOTPWR_{LS}$, RMSSD, SDANN; b) VLF_{LS} and pNN12

In Figure 13 and Figure 14 the paths from the first node to each terminal one are a graphical representation of a set of "if … then" rules. For instance, the path to the terminal node 2 in the Fig. 2a can be read as: "if $TOTPWR_{LS}$ is higher than 8271.86 ms^2 and RMSDD is higher than 15.62 ms, then the subject is classified as normal".

In the models shown in Figure 13, if the selected feature (SDNN; SDANN; $TOTPWR_W$) was lower than a threshold (93.892 ms; 76.869 ms; 6,313.239 ms^2, respectively), the subject was classified as a CHF patient, otherwise as a normal subject.

In the model shown in Figure 14a, the initial variable selected by CART (at node 1 split) was $TOTPWR_{LS}$. The subjects whose $TOTPWR_{LS}$ is lower than 8271.86 ms^2 were correctly classified as CHF patient. CART selected RMSSD for the second node split. In this node split, the subjects whose RMSSD were higher than 15.62 ms were classified as normal. This splitting determined the four false negatives of the classifier. A final classification split is based on SDANN, that is, if it is lower than 106.71 ms, the subject is classified as CHF patient, otherwise as a normal subject.

In the model shown in Figure 14b, the initial variable selected by CART (at node 1 split) was VLF_{LS}. The subjects whose VLF_{LS} is lower than 558.048 ms^2 were correctly classified as CHF patient. CART selected pNN12 for the second node split. In this node split, the subjects whose pNN12 were lower than 36.466 were classified as CHF patients, the others as normal subject. This splitting determined the nine false negatives and the one false positive of the classifier.

3.3.4.1 Performance measurement and comparison with previous studies

In order to compare with previous similar studies, the common performance measure for binary classification were computed as reported in Table 7

Table 7: Binary Classification Performance Measures

Measure	Abbreviation	formula
Accuracy	Acc	$\frac{TP+TN}{TP+TN+FP+FN}$
Precision	Pre	$\frac{TP}{TP+FP}$
Sensitivity	Sen	$\frac{TP}{TP+FN}$
Specificity	Spe	$\frac{TN}{FP+TN}$
Area Under the Curve	AUC	$AUC=\frac{1}{2}\left(\frac{TP}{TP+FN}+\frac{TN}{TN+FP}\right);$

TP: number of CHF patients detected

TN: number of normal subject detected

FP: number of normal subject incorrectly labelled as CHF

FN: number of CHF patients incorrectly labelled as normal.

Table 8 shows the performance measures of the decision tree proposed in this research and of two classifiers proposed by other authors[114, 119].

Table 8: Classification Performance Measurements of the classifiers proposed in the current study and those proposed in previously published papers

Classifier based on single feature	TP #	FN #	TN #	FP #	ACC %	PRE %	SEN %	SPE %	AUC %
SDNN	34	5	69	2	93.6	94.4	87.2	97.2	92.2
SDANN	32	7	71	0	93.6	100	82.1	100	91.0
$TOTPWR_W$	26	9	71	0	91.5	100	74.3	100	87.1
Asyali [114](based on SDNN)	18	4	51	1	93.2	94.7	81.8	98.1	89.9
Classifier based on combination of features	**TP #**	**FN #**	**TN #**	**FP #**	**ACC %**	**PRE %**	**SEN %**	**SPE %**	**AUC %**
$TOTPWR_{LS}$, RMSSD, SDANN	35	4	71	0	96.4	100	89.7	100	94.9
VLF_{LS}, pNN12	26	9	70	1	90.6	96.3	74.3	98.6	86.4
Isler [119]*	29	0	51	3	96.4	90.6	100	94.4	97.2

* based on short-term HRV measures

In both these studies [114, 119] the classifiers were developed using a smaller dataset than in the current study, as they used only the MIT-BIH

Normal Sinus Rhythm Database [112] and the Congestive Heart Failure RR Interval Database [112].

The performance measures of our classifiers are higher than those of Asyali's classifier[114], which used HRV long term measures. Asyali [114] identified SDNN and SDANN as the HRV measures with the highest class separation power and the results in the current study confirm this identification. Moreover, our study showed that $TOTPWR_W$ is the third measure for separation power. This is not in line with Asyali's findings [114], which showed that the $TOTPWR_W$ discrimination power is the second-last. This could be because Asyali used Fisher's Linear Discriminant Analysis (LDA) without proving normal distribution of HRV features. In fact, LDA is strongly affected by non-normality of data [120] and for that reason is expected to provide less accurate information about no-normal measures, such as TOTPWR[121].

The performance measures of our classifier are lower than those of Isler's classifier[119], which used HRV short-term measures. The best combination of features selected by Isler consists of 8 features including sex, FFT-based measures, LS periodogram measures and wavelet entropy measures with a sensitivity rate of 100.00% and a specificity rate of 94.74%[119]. The higher sensitivity rate may be because of the discrimination power of wavelet entropy measures, which have not been considered in this study because they are not standard HRV measures, presumably too complex to understand for most clinicians. Moreover, Isler's classifiers[119] were based on at least 8 features.

As regards the chosen method, this improved intelligibility in comparison to Isler's one [119] and minimized the risk of overfitting in comparison to Asyali's one [114]. In fact, Isler[119] adopted k-nearest-neighbor (KNN) classifiers, which lack the property of the interpretability of induced knowledge [122]. While, Asyali [114] developed a Bayesian Classifier and

the classification is based on the following rule: “a subject with an SDNN value higher (lower) than threshold t_{opt} is classified as normal (abnormal)”. This rule is the same of the tree in Figure 14a, with a slightly different threshold: 93.89 for CART classifier, 91.82 for Bayes classifier. However, Asyaly computed the threshold on the whole dataset and provided no information about probability of misclassification, as he did not use cross-validation approach nor independent test set.

3.3.5 Heart Failure assessment

The results of the data-mining methods adopted consisted into a decision tree like those proposed in. These trees enables the automatic assessment of Heart Failure.

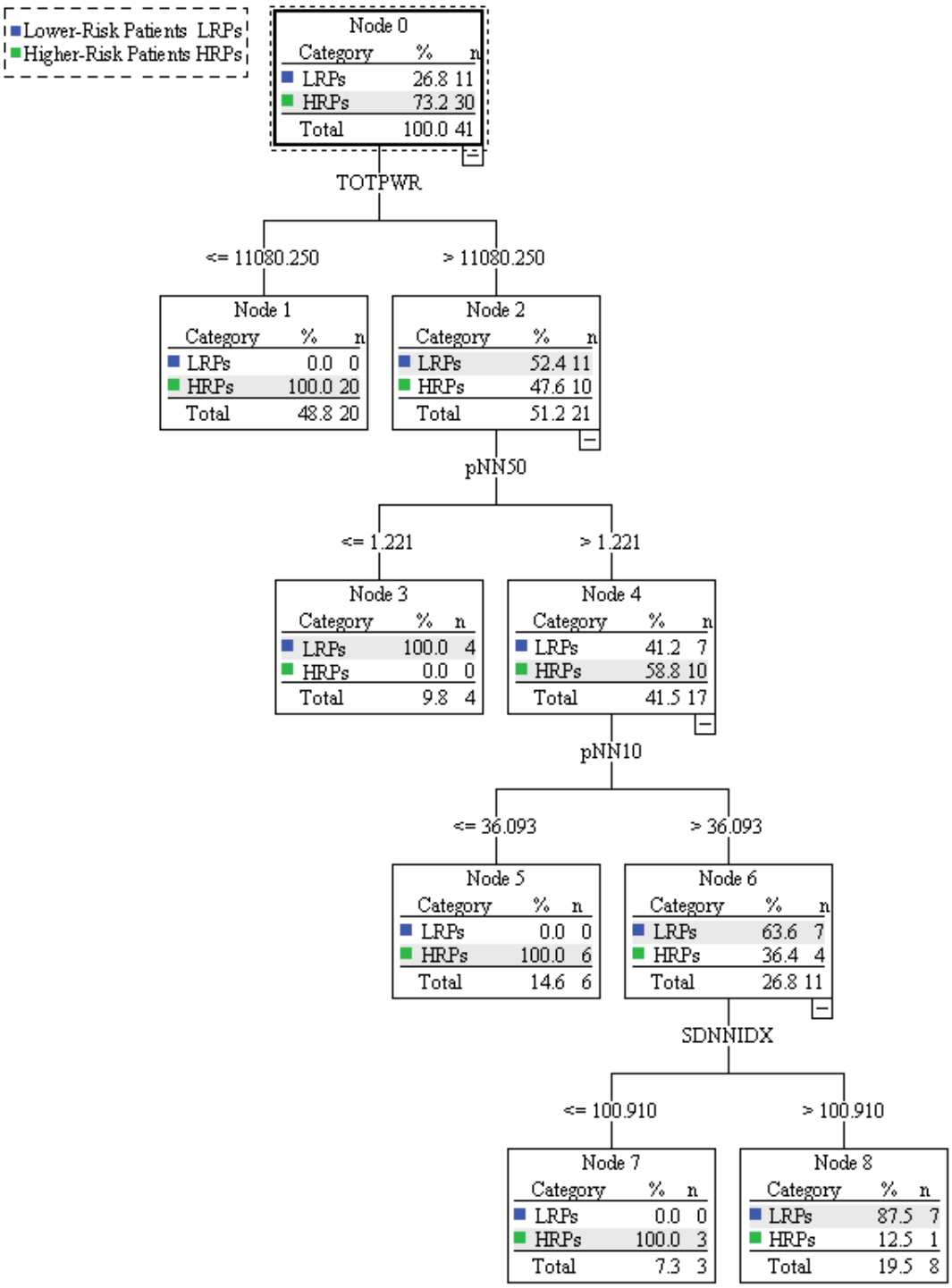

Figure 15: The final model tree for the combination of HRV features: $TOTPWR_L$, pNN50, pNN10, SDNNIDX

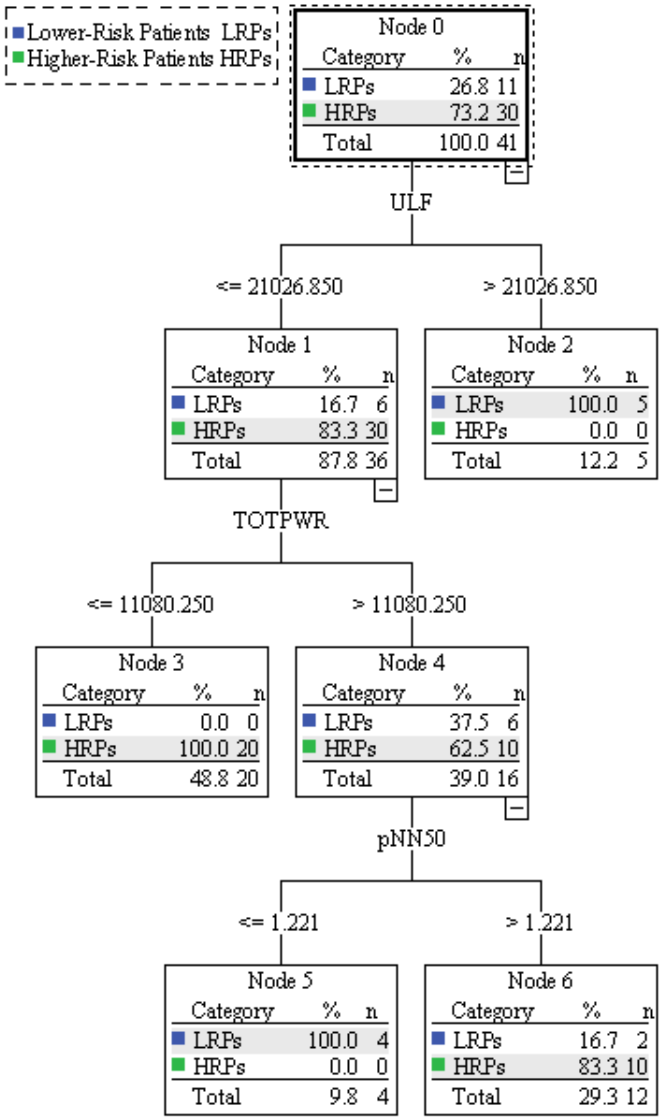

Figure 16: The final model tree for the combination of HRV features: ULF, TOTPWR, pNN50

All the performance measures of these two BSTs, estimated both by 10-fold-crossvalidation and by resubstitution, are reported in Table 9 and Table 10, respectively.

Table 9: Classification performance measurements of the selected classifier estimated by 10-fold-cross-validation

Classifier based on	TP #	FN #	TN #	FP #	ME %	ACC %	SEN %	SPE %	AUC %
TOTPWR, pNN50, pNN10, SDNNIDX	28	2	7	4	14.6	85.4	93.3	63.6	78.5
ULF, TOTPWR, PNN50	28	2	7	4	14.6	85.4	93.3	63.6	78.5
ALL FEATURES	29	0	0	11	27.5	72.5	100	0.0	50.0

Table 10: Classification performance measurements of the selected classifier estimated by resubstitution

Classifier based on	TP #	FN #	TN #	FP #	ME %	ACC %	SEN %	SPE %	AUC %
TOTPWR, pNN50, pNN10, SDNNIDX	29	1	11	0	2.4	97.6	96.7	100	98.3
ULF, TOTPWR, PNN50	30	0	9	2	4.9	95.1	100	81.8	90.9
ALL FEATURES	29	0	0	11	27.5	72.5	100	0.0	50.0

3.4 Discussion and Conclusion

In this chapter, I present the results about the discrimination power of standard long-term Heart Rate Variability (HRV) measures for the detection of Chronic Heart Failure. I analyzed single features and all their possible combinations. It was indicated that the combinations of standard long-term HRV measures $TOTPWR_{LS}$, RMSSD, and SDANN enable distinguishing normal subjects from CHF patients with specificity and sensitivity rates of 100% and 89.74% respectively. The combination of pNN12 and VLF confirms the discrimination power of pNN12 proved by Mietus [116]. The sets of rules of the proposed models are clinically consistent, even if CART did not use any medical a priori knowledge. In fact, the main clinical result of this research is that terminal node classifying as CHF patients are on the left, therefore revealing lower values of the splitting features for CHF patients. This is coherent with the results showed by Bigger [123], Musialik-Lydka [124] and Arbolishvili [125], who stated that standard long-term HRV measures were significantly depressed in CHF patients, compared with normal subjects. It should be emphasized that the findings of Bigger [123] and Arbolishvilli [125] were obtained adopting different methods for power spectral density estimation, while Musialik-Lydka [124] considered only time-domain HRV measures.

Also, the sets of rules of the models for HF assessment are clinically consistent, even if CART does not use any medical a priori knowledge.
In fact, the main clinical result of the research about HF assessment is that terminal node classifying as HRPs are on the left, therefore revealing lower values of the splitting features for severe CHF patients (with the only exception of pNN50). This is coherent with the results showed by Casolo [126], Panina [127] and Arbolishvili. It should be emphasized that the findings of Casolo [126], Panina [127] and Arbolishvili [125] were obtained adopting different methods for power spectral density estimation.

4. Data-mining a data-warehouse for hypertensive patients

4.1 Background

Cardiovascular (CV) diseases are considered one of the most important causes of morbidity and mortality in high developed countries. At this regard, it is important to remember that there is a preclinical and asymptomatic period in which CV diseases can be detected by evaluating target organ damage at cardiac, vascular and renal level and earlier I find CV involvement easier I am able to influence the progression of the disease by therapy.

Indeed, despite there is still a little information on the specific causes of these pathologies, it is well known that some physiological or pathological conditions (Sympathetic Drive) are more frequently related to CV involvement and to CV events. Analysis of heart period variability (HRV) on the basis of routine 24-hour Holter recordings has been shown to provide a sensitive, noninvasive measurement of cardiac autonomic control. Until now clinical studies have shown reduced heart period variability in patients with chronic heart failure, diabetes, and ventricular arrhythmias; moreover, decreased indexes of heart period variability have been shown to be an independent risk factor for mortality in patients after myocardial infarction. By this method, a sympatho-vagal imbalance as evaluated by HRV (Heart Rate Variability) with increased sympathetic activity and reduced vagal tone has been reported in patients with borderline hypertension as well as in hypertensive patients but no data are present in literature on the relation of HRV and different cardiovascular involvement (i.e. cardiac, vascular and renal) and its relationship with their progression and/or regression.

Furthermore, several studies have shown that incidence of CV events can be reduced by therapeutic correction of any of modifiable risk factors, such as hypertension, LDL cholesterol plasma level, diabetes, smoking habit, physical inactivity increase incidence of coronary artery disease. On the

other hand few data are present in the literature on the effect of influence of HRV and the development and progression of CV disease and/or reducing CV risk.

The aim of this chapter was to show the evaluation of the correlation of HRV with asymptomatic development of CV disease at vascular, cardiac and renal level in hypertensive treated patients.

4.2 Methods

4.2.1 Population study

For the present study, among the initial cohort of 12,000 outpatients scheduled in the database of the Campania Salute Network, I selected and recruited all the hypertensive subjects referred to the Hypertension Clinic of the "Federico II" University of Naples from January 2000 which were evaluated by cardiac and carotid ultrasonography and by an 24h Holter ECG and which meet the inclusion criteria. Details on this cohort have been previously described in some papers [128, 129]. Briefly, the Campania Salute network is an open registry collecting information from a network of general practitioners and community hospitals networked with the centre, and providing patients with a centralized data-base including demographics and clinical information.

Exclusion criteria for the present analysis were: diagnosis of secondary resistant and/or uncontrolled hypertension, prevalent CV disease, clinical history of cancer, liver cirrhosis and/or failure, narcotics abuse, lifestyle changes in the last 12 months. Prevalent CV disease was excluded by an ad-hoc committee in the Hypertension Centre, based on patient's history, contact with the referring general practitioner and clinical records documenting the occurrence of disease. Prevalent CV disease was defined as history of previous myocardial infarction or angina or procedures of coronary revascularization, stroke or transitory ischemic attack, congestive

heart failure at the time of the first examination in the outpatient clinic. Thus, the present analysis included 200 hypertensive participants aged from 25 to 88 years (36.5 % women, mean age 62.4±12 yrs), free of prevalent CV disease, who were referred to the Hypertension Clinic of the "Federico II" University of Naples.

The data-base generation of the Campania Salute Network was approved by the Federico II University Hospital Ethic Committee. Signed informed consent for used data for scientific purposes was obtained from all the participant.

4.2.2 Protocol

At the first visit all patients were given a detailed questionnaire inquiring about specifics lifestyle behaviours and smoking habit, in the current study they were categorized as non-smokers, ex-smorkers or smokers.

BP values, clinical, biochemical and ultrasounds parameters were analyzed and recorded at the first visit and during the screening period.

All patients underwent multiple clinical visits and performed baseline and follow-up Echocardiogram and Carotid Ultrasound procedure.

Medical history, physical examination, routine laboratory tests and other diagnostic procedures of the patients were stored in a computerized database.

4.2.3 Measurements and definitions

During the visits, blood pressure, lipid and glucose profile were measured for each patient by standard methods.

Diagnosis and stratification of essential hypertension was performed according to the criteria established by the Guidelines for the Management of Arterial Hypertension.

Systolic and diastolic blood pressure were measured by standard aneroid sphygmomanometer after 5 min rest in the supine position, according to the

current guidelines[130]. Three blood pressure measurements were obtained in the sitting position at 2-min intervals. The averages of these measurements were used for the analysis.

4.2.4 Laboratory Assessment

Serum creatinine, fasting plasma glucose, total-cholesterol, and triglycerides were measured with the standard methods. Glomerular filtration rate (GFR) was calculated by the Modification of Diet in Renal Disease formula[131]. Diabetes was defined as a fasting blood glucose ≥126 mg/dL or active glucose-lowering therapy[132].

4.2.4.1 Echocardiography

Two-dimensional-guided M-mode echocardiograms were performed using a dedicated ultrasound machine (SONOS 5500, Philips) with an ultrasound transducer of 2.5 MHz. The examinations were recorded on a digital recorder and analysed by three independent, trained and experienced physicians. The parameters relative to the left ventricle (LV) were obtained, according to the criteria of the American Society of Echocardiography [133], each as an average of at least three measurements. LV mass was determined by using the formula developed by Devereux and Reichek [134] and divided by the body surface area to calculate LV mass index (LVMi, g/m^2). Echocardiograms were recorded in videotapes, using a standardized protocol, were digitally mastered and read off line by one expert reader under the supervision of a senior faculty member. Measurements were made according to [135].

4.2.4.2 Carotid Ultrasound

B-mode ultrasonography of carotid arteries was performed with patients in the supine position with the neck extended in mild rotation. The scanning protocol was performed with an ultrasound device (SONOS 5500, Philips)

equipped with a 7.5-MHz high-resolution transducer with an axial resolution of 0.1 nm. Examinations were recorded on S-VHS videotapes. All measurement were analysed by three different trained experienced physicians. An average of two readings were considered for subsequent calculations. The accuracy of determinations was evaluated as previously described by Lembo et al. [136]. The maximum arterial IMT (IMT max) in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation, and proximal internal carotid artery were estimated offline with an image processing workstation.

4.2.5 Assessment of target organ damage

Cardiac Involvement was evaluated as Left Ventricular Hypertrophy (LVH) which was diagnosed if LVMi exceeded 110 g/m^2 in female and 125 g/m^2 in male[137]. Intraoperator and interassay variability were 5% and 6%, respectively [138]

Vascular Involvement was assessed as Carotid artery atherosclerosis as an increased intimal plus medial thickness (IMT) by B-mode ultrasonography. IMT values between 0.9 and 1.3 mm were defined "thickening" and those higher than 1.3 mm as "plaque".

Chronic kidney disease was assessed by Glomerular filtration rate (GFR) using the simplified MDRD formula[139] and involvement was quantify as grade 1 to 3. The patients were stratified by the glomerular filtration rate (GFR) in three groups: Group 1: increased or normal GFR ($GFR \geq 90$ mL/min/1.73 m^2); Group 2: mild GFR ($60 < GFR < 90$ mL/min/1.73 m^2); Group 3: moderate and severe GFR ($GFR \leq 60$ mL/min/1.73 m^2)[140].

4.2.6 Processing 24-Hour Holter Recordings

On 2 consecutive days, patients underwent 24-hour ambulatory BP monitoring, 24-hour ECG Holter recording. The recorders were applied between 9 and 11 AM on a working day, and patients were asked to follow

as closely as possible their usual daily activities during each monitoring session. They were asked to stay in bed from 11 PM to 7 AM, and all reported to have slept normally during the nights they were monitored.

The series of normal to normal (NN) beat intervals were obtained from ECG recordings using OSAS, an open-source software for QRS detection and beat classification[141].

Standard long-term HRV analysis on nominal 24-h recordings according to International Guidelines was performed [113].

The HRV analysis was performed using PhysioNet's HRV Toolkit[112]. The NN/RR ratio was computed as the fraction of total RR intervals classified as normal-to-normal (NN) intervals. This ratio has been used as a measure of data reliability, excluding records with a ratio less than a threshold. The authors chose a threshold of 80%, as it was a satisfactory trade-off between numbers of included subjects and quality of NN signals.

All the computed basic time- and frequency-domain HRV measures were widely used in the literature[113]

A number of standard statistical time-domain HRV measures are calculated: Average of all NN intervals (AVNN), standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments of a 24-h recording (SDANN), mean of the standard deviations of NN intervals in all 5-min segments of a 24-h recording (SDNN IDX), square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), percentage of differences between adjacent NN intervals that are longer than 50 ms (pNN50).

The frequency-domain HRV measures rely on the estimation of power spectral density (PSD) computed, in this work, by Lomb-Scamble periodogram [118]

After PSD estimation, six standard frequency-domain HRV measures were calculated: total spectral power of all NN intervals up to 0.4 Hz (TOTPWR), between 0 and 0.003 Hz (ULF), between 0.003 and 0.04 Hz (VLF), between 0.04 and 0.15 Hz (LF), and between 0.15 and 0.4 Hz (HF), ratio of low to high frequency power (LF/HF).

4.2.7 Statistical Analysis

Data were analysed by the use of PASW software (version 18; SPSS, Chicago, IL, USA).

Univariate differences were analysed using Kruskal-Wallis test for HRV measures, ANOVA for the other continuous variables (for instance age, IMT, etc) and χ test for the categorical variables (for instance sex, smoking). For each HRV measure, which differs significantly among the three groups, an adjusted model was proposed by performing a multinomial logistic regression. For each factor, the coefficient of the estimated regression model (β), the confidence interval for β at 95% and the corresponding statistical significance (p) are presented.

4.3 Results

200 patients were analysed (127 male and 73 female). Demographic, clinical and laboratory characteristics of all the study population are shown in Table 11. The prevalence of diabetes in our study population was 18%. These patients were treated with anti-diabetic drugs (insulin, sulfonylureas, thiazolidinediones).

Table 11: Characteristics of the study sample of patients

Variables	Values
Age (years)	62.4±12
IMT	2.24±1.56
LVMIDP	130.2±30.8
MDRD	77.3±18.5

Variables	Values
Diastolic BP (mmHg)	75.6±11.9
Systolic BP (mmHg)	133±22.6
Pulse pressare (mmHg)	57.5±17.8
Fasting blood glucose (mmHg)	102.9±24
Total Cholesterol (mg/dl)	186±40.5
Sex (male/female, %)	63.5/46.5
Diabetes (yes / no, %)	18 / 82
Fam Hypertension (yes/no, %)	57/43
Fam. Ictus (yes/no, %)	18/82
Smokers (yes/ex/no, %)	18/21/62
Beta-blockers(yes/no, %)	33.5/66.5
Alfabeta-blockers (yes/no, %)	10/90
Alpha-blockers (yes/no, %)	8/92
Diuretics (yes/no, %)	43/57
ACE-inhibitor (yes/no, %)	37/63
Dihydropyridine (yes/no, %)	26/74
Vascular Involvement (no/ thickening/plague, %)	24/60/76
Kidney Involvment (Group 1/ 2 /3 %)	13.5/11/86.5
Left Ventricular hypertrophy (yes/no)	40.5/59.5

Table 12 shows the characteristic of the study sample of patients categorized by GFR in three groups. The Group 3 is significantly older than the others and has a significantly higher proportion of patients taking diuretic. Diastolic Blood Pressure, Systolic Blood Pressure and Pulse Pressure values were significantly higher in Group 2, where IMT value were significantly lower in Group 1.

Table 12: Characteristics of the study sample of patients stratified by GFR

Variables	Group 1	Group 2	Group 3	p-value
Age (years)	56±11.4	63±11.6	69.7±9.2	0.000
IMT	1.8±0.76	2.23±1.21	2.9±2.85	0.008
LVMIDP	124.3±25.9	132.8±32.1	128.9±30.9	0.263

Variables	Group 1	Group 2	Group 3	p-value
MDRD	101.9±11.8	74.3±8.7	51.5±6.2	0.000
Diastolic BP (mmHg)	73.2±13.8	77.3±11.4	72.6±9.6	0.042
Systolic BP (mmHg)	124.5±23.1	137.3±19.7	129.5±27	0.002
Pulse pressare (mmHg)	51.3±14	60±16.8	57±23.2	0.015
Fasting blood glucose (mmHg)	99.7±31.9	102.9±19.9	107.4±23.5	0.368
Total Cholesterol (mg/dl)	178.9±36	187.7±40.4	190.3±45.2	0.358
Sex (male/female, %)	64.6/35.4	64.2/35.8	59.4/40.6	0.868
Diabetes (yes / no, %)	18.8/81.2	16.7/83.3	21.9/78.1	0.783
Fam. Hypertension (yes/no, %)	52.1/47.9	58.3/41.7	59.4/40.6	0.728
Fam. Ictus (yes/no, %)	20.8/79.2	18.3/81.7	12.5/87.5	0.629
Smokers (yes/ex/no, %)	27.1/16.7/56.2	14.2/22.5/63.3	15.6/18.8/65.6	0.363
Beta-blockers (yes/no, %)	31.3/68.7	34.2/65.8	34.4/65.6	0.931
Alfabeta-blockers (yes/no, %)	10.4/89.6	11.7/88.3	3.1/96.9	0.357
Alpha-blockers(yes/no, %)	6.3/93.7	6.7/93.3	15.6/84.4	0.221
Diuretics (yes/no, %)	35.4/64.6	40.8/59.2	62.5/37.5	0.042
ACE-inhibitor (yes/no, %)	33.3/66.7	40/60	31.3/68.7	0.550
Dihydropyridine (yes/no, %)	25/75	25/75	31.3/68.7	0.761
Kidney Involvement (Group 1/ 2 /3, %)	0/0/100	0/100/0	100/0/0	0.000
Vascular Involvement (plague/thickening/no, %)	68.7/12.5/18.8	75.9/10.8/13.3	84.4/9.4/6.2	0.553
Left Ventricular hypertrophy (yes/no)	50/50	62.5/37.5	62.5/37.5	0.306

Table 13 shows the mean value of HRV measures in the groups. The three groups differed significantly in LF/HF. This difference persisted even in the adjusted model, as shown in Table 14.

Table 13: Comparisons of HRV measurement in the group of patients stratified by GFR

	MDRD>90				90>MDRD>60				MDRD<60				
	Mean	**Median**	**Percentiles**		**Mean**	**Median**	**Percentiles**		**Mean**	**Median**	**Percentiles**		
			25	**75**			**25**	**75**			**25**	**75**	**p-value**
AVNN	859.656	848.931	784.875	915.911	866.782	852.402	772.551	953.323	890.917	875.997	806.343	963.397	0.358
SDNN	125.662	119.542	102.303	145.981	119.634	111.134	92.211	141.291	118.098	113.797	98.261	141.068	0.309
SDANN	113.399	108.585	90.246	137.020	106.970	99.823	78.398	129.377	106.366	105.624	86.031	132.446	0.331
SDNN IDX	51.926	51.430	43.872	58.769	51.192	47.101	40.778	61.044	46.204	45.040	36.859	58.248	0.244
RMSSD	32.572	30.060	24.496	37.738	35.615	30.525	22.410	42.082	35.971	33.665	24.671	42.061	0.501
pNN50	8.825	7.678	3.942	11.742	11.169	7.884	2.732	17.711	11.694	10.063	4.069	12.851	0.661
TOTPWR	18224.030	16124.350	11012.100	23626.200	17528.314	13783.600	9042.495	21606.800	17473.407	15175.150	10303.480	24712.600	0.355
ULF	14919.459	12378.550	8864.230	18678.700	14139.891	10707.800	7102.665	18480.050	14610.106	12001.300	8215.475	20216.800	0.359
VLF	1815.051	1592.025	1195.170	2367.555	1865.617	1421.585	961.295	2404.685	1404.330	1259.530	812.876	1958.985	0.110
LF	860.764	711.187	485.837	1102.005	822.330	600.558	370.216	916.729	678.619	577.239	373.462	925.431	0.154
HF	628.760	471.256	298.766	724.492	700.487	493.440	201.829	801.501	780.358	549.748	288.798	1230.165	0.436
LF/HF	1.741	1.439	1.168	2.099	1.508	1.253	0.910	1.751	1.012	0.867	0.724	1.251	**0.000**

Table 14: Adjusted model for all the variables for the relationship between LF/HF and the groups according to MDRD; the group 3 (MDRD < 60) is the reference in this model

								95% Confidence Interval for Exp(B)	
		B	Error std	Wald	df	Sig.	Exp(B)	Lower bound	Upper bound
1	Intercept	5.856	2.512	5.434	1	**.020**			
	LF/HF	.977	.459	4.522	1	**.033**	2.655	1.079	6.531
	SystolicBP	-.005	.011	.213	1	.645	.995	.973	1.017
	Age	-.104	.028	14.351	1	**.000**	.901	.854	.951
	No Hypertensive Familiarity	1.153	.536	4.635	1	**.031**	3.168	1.109	9.050
2	Intercept	.322	2.225	.021	1	.885			
	LF/HF	.993	.436	5.188	1	**.023**	2.699	1.149	6.341
	SystolicBP	.021	.010	4.226	1	**.040**	1.021	1.001	1.042
	Age	-.051	.024	4.473	1	**.034**	.950	.906	.996
	No Hypertensive Familiarity	.758	.448	2.862	1	.091	2.134	.887	5.138

Among all the variables, which were considered in the adjusted model, the multinomial logistic regression selected age, hypertensive familiarity, and systolic blood pressure. Higher values of LF/HF are associated with an increased probability that a subject belongs to the Groups 1 or 2 rather than to the Group 3 (odd ratio 2.655 and 2.699 respectively). Older age is associated with a decreased probability of being in Group 1 or 2 (odd ratio 0.901 and 0.950 respectively). No hypertensive familiarity is associated with an increased probability of belonging to Group 1 (odd ratio 3.168). Higher value of systolic blood seems to be associated with a slightly increased probability of belonging to Group 2 (odd ratio 1.021).

Table 15 shows the characteristic of the study sample of patients categorized by IMT in three groups. The Plague Group is significantly older than the others. LVMIDP values were significantly higher in the Plague Group and the proportion of patient with LVH was significantly higher. A significantly higher proportion of patients with hypertensive familiarity was assessed in Thickening Group. A significantly higher proportion of patients taking beta-blockers was assessed in the Group with no vascular involvement.

Table 15: Characteristics of the study sample of patients stratified by IMT

Variable	No Vascular Involvement	Thickening	Plague	p-value
Age (years)	47.7±13	57±9.4	65.8±9.7	**0.000**
IMT	0.9±0.1	1.19±0.08	2.62±1.61	**0.000**
LVMIDP	109.5±18.3	126.7±32.4	134.3±30.7	**0.000**
MDRD	83.7±16.9	81.2±17.4	75.5±18.6	0.060
Diastolic BP (mmHg)	76.3±10.4	73.4±18.1	75.7±11	0.663
Systolic BP (mmHg)	130.9±18.7	124±32.4	134.7±21	0.105
Pulse pressare (mmHg)	54.6±14.4	50.6±19.4	59±17.8	0.082
Fasting blood glucose (mmHg)	98.5±20	95.7±21.5	104.7±24.7	0.156
Total Cholesterol (mg/dl)	182.1±36.6	192±38.2	185.8±41.3	0.691
Sex (male/female, %)	63/37	45.5/54.5	66.2/33.8	0.167
Diabetes (yes / no, %)	11.1/88.9	4.5/95.5	21.2/78.8	0.100
Fam Ipertensione (yes/no, %)	63/37	81.8/18.2	52.3/47.7	**0.026**
Fam, Ictus (yes/no, %)	14.8/85.2	31.8/68.2	16.6/83.4	0.197
Smokers (yes/ex/no, %)	14.8/11.1/74.1	27.3/9.1/63.6	16.6/23.8/59.6	0.235
Beta-blockers(yes/no, %)	55.6/44.4	27.3/72.7	30.5/69.5	**0.032**
Alfabeta-blockers(yes/no, %)	3.7/96.3	13.6/86.4	10.6/89.4	0.456
Alpha-blockers(yes/no, %)	3.7/96.3	9.1/90.9	8.6/91.4	0.674
Diuretics (yes/no, %)	33.3/66.7	36.4/63.6	45.7/54.3	0.392

Variable	No Vascular Involvement	Thickening	Plague	p-value
ACE-inhibitor (yes/no, %)	37/63	36.4/63.6	37.1/62.9	0.998
Dihydropyridine (yes/no, %)	25.9/74.1	18.2/81.8	27.2/72.8	0.669
Kidney Involvment (Group 1/ 2 /3 %)	7.4/59.3/33.3	13.6/59.1/27.3	17.8/60.3/21.9	0.553
Vascular Involvement (plague/thickening/no, %)	0/0/100	0/100/0	100/0/0	0.000
Left Ventricular hypertrophy (yes/no)	22.2/77.8	50/50	67.5/32.5	**0.000**

Table 16 shows the mean value of HRV measures in the groups. The three groups differed significantly in SDNN, SDANN, Total Power, LF, and LF/HF. The adjusted models confirmed these difference in the value of SDNN and SDANN.

In fact, as shown by Table 17 and Table 18 higher value of SDNN and SDANN are associated with an increased probability that a subject had no vascular involvement rather than plague (odd ratio 1.017 in both cases). Moreover, these models confirms that older age is associated with a vascular involvement.

Table 16: Comparisons of HRV measurement in the group of patients stratified by IMT

	No Vascular invovement				Thickening				Plague				
	Mean	**Median**	**Percentiles**		**Mean**	**Median**	**Percentiles**		**Mean**	**Median**	**Percentiles**		
			25	**75**			**25**	**75**			**25**	**75**	**p-value**
AVNN	826.684	812.136	747.978	910.820	842.253	820.497	750.911	955.632	880.375	865.860	797.949	952.010	0.074
SDNN	140.284	133.950	107.341	168.065	121.747	115.265	94.650	145.492	117.224	111.984	93.737	136.941	**0.039**
SDANN	129.041	125.517	89.704	155.750	110.781	102.201	82.055	137.995	104.383	99.402	80.588	124.070	**0.033**
SDNN IDX	58.381	52.787	44.646	71.452	50.739	48.891	43.382	56.469	49.149	47.437	39.186	59.529	0.060
RMSSD	36.311	30.926	26.458	41.442	30.737	29.744	22.262	33.683	35.309	30.656	22.703	41.714	0.310
pNN50	12.132	8.123	5.739	15.845	9.164	6.089	2.860	11.039	10.656	8.439	3.099	15.453	0.300
TOTPWR	24097.15	19770.90	12982.60	30746.73	17583.21	14497.00	9953.56	21881.20	16555.28	13889.30	9328.20	21254.72	**0.043**
ULF	19533.87	16191.40	9760.808	24292.95	14453.19	11822.15	8122.05	18502.50	13477.22	11035.00	7340.168	17850.97	0.074
VLF	2536.076	2009.720	1123.815	3013.678	1745.842	1513.635	1114.73	1859.600	1649.354	1343.890	960.970	2250.945	0.079
LF	1237.769	921.762	511.003	1723.410	818.685	687.722	494.334	933.637	730.339	570.636	362.265	934.279	**0.009**
HF	789.434	541.702	294.196	1215.156	565.502	499.355	185.849	596.352	698.375	477.522	231.957	913.954	0.485
LF/HF	1.898	1.556	1.078	2.358	2.019	1.551	1.192	2.685	1.333	1.131	0.826	1.679	**0.001**

Table 17: Adjusted model for all the variables for the relationship between SDNN and the groups according to IMT; the Plague Group is the reference in this model

							95% Confidence Interval for Exp(B)	
		B	Error std	Wald	df	Sig.	Exp(B)	Lower bound	Upper bound
1	Intercept	5.580	1.743	10.250	1	**.001**			
	SDNN	.017	.007	5.305	1	**.021**	1.017	1.003	1.032
	Age	-.166	.029	32.036	1	**.000**	.847	.800	.897
	No Hypertensive Familiarity	.261	.544	.230	1	.632	1.298	.447	3.774
2	Intercept	2.534	1.619	2.452	1	.117			
	SDNN	.008	.007	1.660	1	.198	1.009	.996	1.022
	Age	-.083	.025	11.254	1	**.001**	.920	.876	.966
	No Hypertensive Familiarity	-1.100	.592	3.454	1	.063	.333	.104	1.062

Table 18: Adjusted model for all the variables for the relationship between SDNN and the groups according to IMT; the Plague Group is the reference in this model

							95% Confidence Interval for Exp(B)	
		B	Error std	Wald	df	Sig.	Exp(B)	Lower bound	Upper bound
1	Intercept	5.763	1.696	11.548	1	**.001**			
	SDANN	.017	.007	5.824	1	**.016**	1.017	1.003	1.031
	Age	-.166	.029	32.107	1	**.000**	.847	.800	.897
	No Hypertensive Familiarity	.277	.547	.257	1	.612	1.320	.452	3.857
2	Intercept	2.492	1.586	2.467	1	.116			
	SDANN	.010	.006	2.219	1	.136	1.010	.997	1.023
	Age	-.083	.025	11.227	1	**.001**	.920	.876	.966
	No Hypertensive Familiarity	-1.082	.593	3.325	1	.068	.339	.106	1.084

Table 19 shows the characteristic of the study sample of patients with and without LVH. The LVH Group is significantly older than the other. IMT values were significantly higher in the LVH Group and the proportion of patient with Vascular Involvement was significantly higher. A significantly higher proportion of patients taking diuretics and patients suffering from

diabetes was assessed in LVH Group. The value of SBP and PP were significantly higher in the VLH group.

Table 19: Characteristics of the study sample of patients with and without LVH

	No VLH	VLH	
Age (years)	56.9±11.9	66.1±10.5	**0.000**
IMT	1.81±0.92	2.52±1.81	**0.000**
LVMIDP	105±13.6	147.3±27.2	**0.000**
MDRD	79.8±17.7	75.5±18.8	0.071
Diastolic BP (mmHg)	73.8±11.9	76.7±11.8	0.221
Systolic BP (mmHg)	126±25	137.7±19.3	**0.001**
Pulse pressare (mmHg)	52.2±17.8	61.1±16.8	**0.002**
Fasting blood glucose (mmHg)	99.9±23.4	104.8±24.2	0.055
Total Cholesterol (mg/dl)	191±38.1	182.6±41.6	0.175
Sex (male/female, %)	61.7/38.3	64.7/35.3	0.668
Diabetes (yes / no, %)	9.9/90.1	23.5/76.5	0.014
Fam Ipertensione (yes/no, %)	60.5/39.5	54.6/45.4	0.410
Fam. Ictus (yes/no, %)	18.5/81.5	17.6/82.4	0.875
Smokers (yes/ex/no, %)	21/22.2/56.8	15.2/19.3/65.5	0.419
Beta-blockers(yes/no, %)	38.3/61.7	30.3/69.7	0.238
Alfabeta-blockers(yes/no, %)	8.6/91.4	10.9/89.1	0.597
Alpha-blockers(yes/no, %)	6.2/93.8	9.2/90.8	0.432
Diuretics (yes/no, %)	30.9/69.1	51.3/48.7	**0.004**
ACE-inhibitor (yes/no, %)	30.9/69.1	41.2/58.8	0.138
Dihydropyridine (yes/no, %)	21/79	29.4/70.6	0.182
Kidney Involvment (Group 3/ 2 /1 %)	14.8/55.6/29.6	16.8/63/20.2	0.306
Vascular Involvement (plague/thickening/no, %)	60.5/13.6/25.9	85.8/9.2/5	**0.000**
Left Ventricular hypertrophy (yes/no)	0/100	100/0	0.000

Table 20 shows the comparison of HRV measures in the patients with and without VLH. The two groups differed significantly in AVNN and LF/HF.

The adjusted model, such as the one reported in Table 21, did not confirm these difference, and showed that other variable were associated with VLH such as Age, Systolic Blood Pressure, Cholesterol, and Diuretics assumption.

Table 20: Comparisons of HRV measurement in the group of patients with and without LVH

	No LVH				LVH				
	Mean	Median	Percentiles		Mean	Median	Percentiles		
			25	75			25	75	P Value
AVNN	845,595	827,887	772,150	915,004	884,819	867,100	791,728	963,805	**0,046**
SDNN	123,743	118,484	101,663	143,219	118,856	113,243	92,795	142,407	0,253
SDANN	111,605	107,254	88,133	131,307	106,245	99,402	80,050	129,532	0,292
SDNN IDX	51,820	49,334	43,116	60,694	49,719	48,334	38,678	58,396	0,162
RMSSD	32,613	29,032	22,774	36,409	36,527	32,875	23,345	42,254	0,087
pNN50	9,808	6,961	3,037	11,751	11,292	9,214	3,391	17,050	0,125
TOTPWR	18505,554	16012,800	10952,300	21896,700	17128,994	14063,700	9098,123	22697,050	0,302
ULF	15068,814	12109,900	8462,103	18527,900	13948,491	11534,400	7132,508	18655,575	0,355
VLF	1882,325	1659,880	1082,100	2390,558	1709,805	1343,890	938,679	2086,480	0,137
LF	894,710	711,065	429,249	1090,893	749,921	559,352	371,320	911,662	0,078
HF	659,714	476,406	205,448	747,982	720,787	504,430	266,741	964,938	0,229
LF/HF	1,782	1,643	1,038	2,095	1,282	1,040	0,822	1,505	**0,000**

Table 21: Adjusted model for all the variables for the relationship between LF/HF and the groups according to LVH; the LVH Group is the reference in this model

	B	E.S.	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B) Lower bound	Lower bound
LF/HF	-.200	.207	.935	1	.334	.819	.546	1.228
Age	.068	.017	15.394	1	**.000**	1.070	1.035	1.107
Systolic BP	.029	.009	11.260	1	**.001**	1.030	1.012	1.047
Cholesterol	-.009	.004	4.334	1	**.037**	.991	.983	.999
Diuretics	-.779	.346	5.081	1	**.024**	.459	.233	.903
Intercept	-5.240	1.804	8.441	1	**.004**	.005		

4.4 Discussion

In this study I evaluated in hypertensive patients the effects of complete CV involvement on cardiac autonomic control, as assessed by means of heart period variability analysis. Power spectral analysis of 24-hour electrocardiographic monitoring was performed in 200 hypertensive patients in basal conditions. At this same times, patients underwent 24-hour blood pressure monitoring, echocardiographic and carotic ultrasonographic study evaluations, and routine laboratory evaluations in order to calculate VFG with MDRD formula.

The LF/HF, shown as a marker of the sympatho-vagal balance, decreased significantly in the group with organ damage. However, when adjusted with the other variable, in particular Age, this difference is significant only for Kindney organ damage. SDNN and SDANN, index of the overall heart rate modulation, decreased significantly in the group of patients with Plague, also when adjusted considering the other variables.

5. Long-term survival prediction

5.1 Introduction

Over the last three decades a range of risk factors for mortality among community-dwelling people has been identified [142-156]. Understanding the factors that increase the risk of mortality may be promoting survival, as well as helpful in promoting health and well-being, in later life. The majority of previous studies on mortality were performed using conventional statistical techniques, for example, regression analysis, in order to identify factors that increase, or decrease, the risk of mortality [157]. For reasons of statistical power and computational complexity, conventional statistical techniques enables only a limited number of potential risk factors to be examined [157]. Some recent studies have applied data-mining techniques, in particular, in a previous study [158] a genetic algorithm and Cox regression were combined to identify risk factors among a wide number of variables.

The aim of this study was to develop a CART model which can predict 15 year survival with acceptable sensitivity and specificity in order to provide further knowledge about previously identified risk factors.

5.2 Methods and materials

Data were derived from the Nottingham Longitudinal Study of Activity and Ageing (NLSAA)[159]. NLSSA is an ongoing survey of activity, health and well-being conducted within a representative sample of 1299 community-dwelling people originally aged 65 and over, of whom 1042 (406 men; 636 women) agreed to participate (response rate = 80 %). The baseline survey was conducted between May and September 1985, and information on mortality within the sample was provided by the UK National Health Service Central Register, where all UK deaths are recorded and which supplied copies of all the death certificates as they accrued. Interview data collected from respondents included information on

cognition, physical health, psychological wellbeing, perceptions of health and wellbeing, and customary physical activity, and are described in detail elsewhere[159].

I considered the set of variables which were identified in [158] as predictors of long-term mortality. In this previous study [158], genetic algorithms were used to select the combination of variables that maximized the goodness of fit for the Cox regression model. Table 21 and Table 22 show the selected continuous and categorical variables, respectively.

Table 22: Descriptives of continuous variables identified as Risk Factors for 15-Year Mortality among community-dwelling older people [158].

Continuous Variables	Range	Mean	Median
Age at 85 interview (computed from borndate)	65-99	75.63	75
Number of living great-grandchildren	0-26	1.12	0
Dose of hypnotic drug being taken (mg)	0-1300	28.08	0
Hypnotic drug taken for (n) years	0-47	1.46	0
Maximum handgrip strength	43-617	254.75	237
Maximum handgrip strength for dominant hand	29-612	246.43	231
Maximum handgrip strength for non-dominant hand	27-617	235.20	220
Right Handgrip strength at first measurement(kg)	2-57	23.25	22
Right Handgrip strength at third measurement(kg)	3-63	25.33	24
Left Handgrip strength at third measurement (N)	22-556	222.73	208
Number of floors in accommodation	1-3	1.67	2

I developed a binary classifier based on CART [160] in order to predict 15-year mortality. The information on mortality within the sample was provided by the UK National Health Service Central Register and for the purpose of this study were update to 2000, 15 years after the baseline

survey (1985). The values of the input variables, summarized in Table 22 and Table 23, were collected in the baseline survey conducted in 1985.

Table 23: Descriptives of categorical variables identified as Risk Factors for 15-Year Mortality among community-dwelling older people [158]

Categorical Variables	Category	N	%
Permission to access OPCS (Office for Census and Population Studies) files?	Yes, permission given	1,022	98
	No, permission refused	20	2
Activity compared with that of age group	1- Much more active	125	13
	2- More active	398	41
	3- About as active	225	23
	4- Less active	154	16
	5- Much less active	59	6
How much happiness in your life today?	A lot	322	33
	Quite a lot	230	24
	A little	238	24
	None	184	19
Joint pain causing difficulty in carrying bags?	No difficulty	783	83
	Yes, difficult	160	17
Joint pain causing difficulty in walking?	No difficulty	691	69
	Yes, difficult	306	31
Ability to raise £200 in an emergency	No difficulty	714	71
	A Little Difficulty	121	12
	A Lot of Difficulty	102	10
	Impossible to raise	73	7
Time since last visited the dentist	Last week	18	2
	Last month	34	3
	Within last six months	89	9
	> 6 months ago	876	86
Time since last visited the optician	Last week	18	2
	Last month	30	3

Categorical Variables	Category	N	%
	Within last six months	164	16
	> 6 months ago	805	79
Time since last visited the social worker	Last week	7	1
	Last month	18	2
	Within last six months	31	3
	> 6 months ago	959	94
Reported stomach troubles?	No problem	748	73
	Yes, problem	283	27
Reported pain in left anterior chest?	No	959	98
	Yes	18	2
Reported chest pain in no specific position?	No	968	99
	Yes	9	1

In order to optimize the tree performance, an a priori classification cost could be assigned. I examined different misclassification cost ratios c(1|2)/ c(2|1): 1/1, 1.5/1, 2/1, 2.5/1. For instance, a misclassification cost ratio of 2/1 means that the cost of misclassifying a survivor was twice as great as that of misclassifying a participant who had died. Stopping rules govern the size of the tree.

The misclassification risks are estimated by 10-fold cross-validation methods. The cross-validation method consists of dividing the sample into a number of folds and generating tree models excluding the data from each fold in turn. For each model, the misclassification risk is estimated by applying the tree to the fold excluded in generating it. The risk estimate for the final tree is calculated as the average of the risks for all of the trees[160].

The performance of each classifier against the whole dataset is assessed using the common measures for binary classification, calculated as reported

in Table 24. I selected the classifiers with a high sensitivity value (higher than 75%) and acceptable specificity values (higher than 65%).

Table 24: Performance Measurement

Measure	Abbreviation	formula
Accuracy	ACC	$\frac{TP+TN}{TP+TN+FP+FN}$
Sensitivity	SEN	$\frac{TP}{TP+FN}$
Specificity	SPE	$\frac{TN}{FP+TN}$
Positive predictive value	PPV	$\frac{TP}{TP+FP}$
Negative predictive value	NPV	$\frac{TN}{TN+FN}$;

Where:

TP (true positives) is the number of survivors, correctly classified by the system,

TN (true negatives) is the number of participants who have died, correctly classified by the system,

FP (false positives) is the number of participants who have died, incorrectly labelled as survival by the system,

FN (false negatives) is the number of survivors, incorrectly

5.3 Results

The performance measurement, including risk estimation and confusion matrix values, for the developed classifier which achieved the best performance are summarized in Table 25.

Table 25: performance of the selected model

Cost	Alive		Dead		Risk						
Ratio	**TP**	**FN**	**TN**	**FP**	**Estimate**	**Error**	**Acc**	**Sen**	**Spec**	**PPV**	**NPV**
2.5:1	235	73	487	247	0.517	0.023	69.3%	76.3%	66.3%	48.8%	87.0%

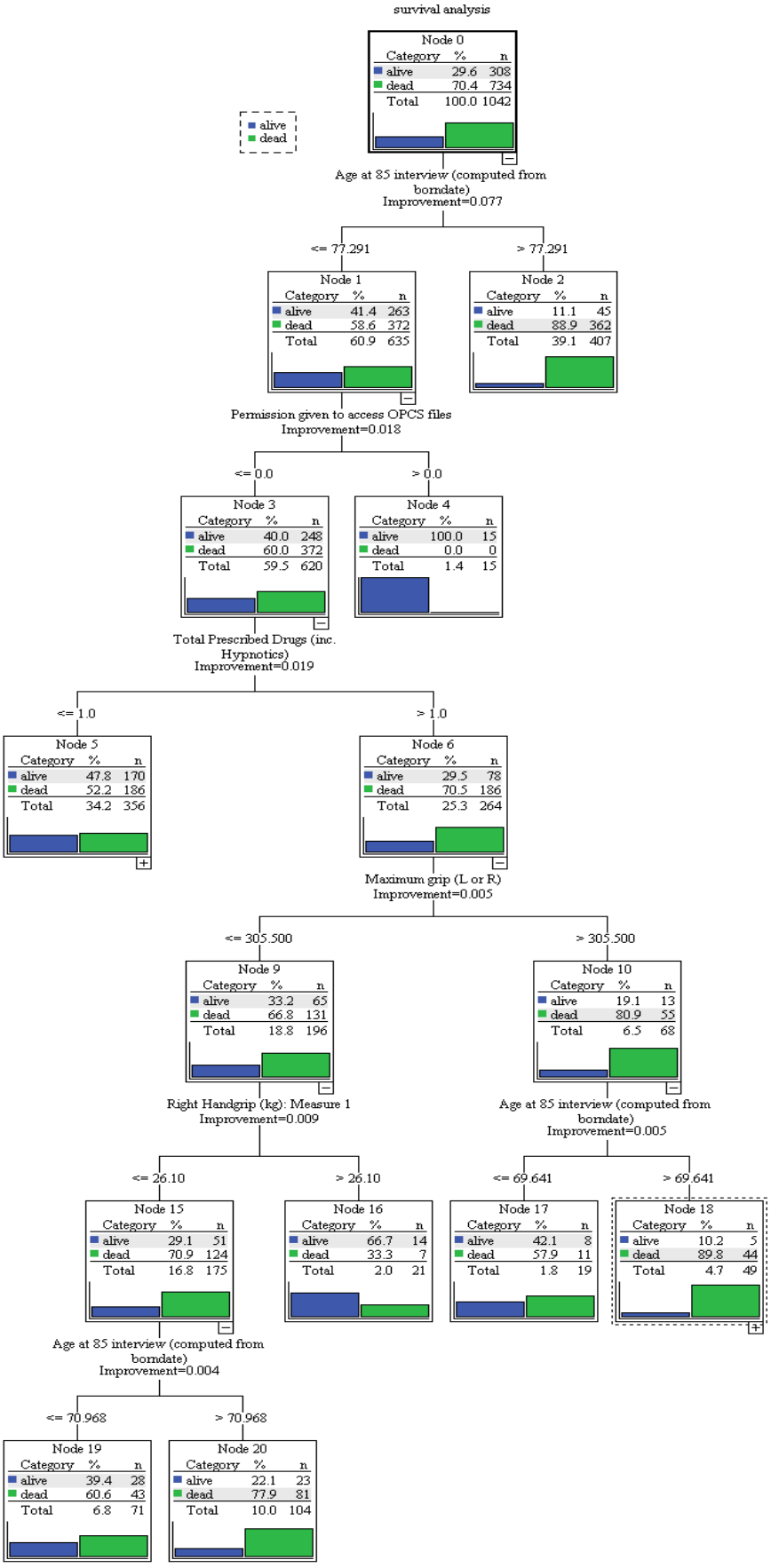

Figure 17: selected model for long-term survival prediction

The model considers age, permission given to access OPCS file, dose of

total prescribed drugs, the maximum grip for both hands, and right handgrip strength. The initial variable selected by CART was age (with a cut-off of 77.291), people older than 77.291 year were classified as not surviving.

CART selected Permission to access OPCS (Office for Census and Population Studies) files in node 2 splitting: people who refused this permission were predicted to survive, the others were split according to the dose of total prescribed drug being taken, if it was not more than 1.00 mg, they were predicted to survive, otherwise they were classified according to their handgrip strength and age.

5.4 Discussion

This study integrated the results of the previous research [157, 158] which used Cox regression combined with Genetic Algorithms (CoRGA) to identify risk factors for long-term mortality among older people. The CART analysis was performed in order to improve the knowledge about the importance of the identified factor as a predictor of mortality.

Moreover, using the CART analysis, I observed the range of risk factor values which are associated with decreased or increased 15-year-mortality. I observed that:

Being aged more than 77.291 was associated with increased mortality;

in people aged 65-72 taking drugs / medication of less than 1 mg is associated with decreased mortality,

In people aged 65-72 who took a dose of drug higher than 1 mg, an increased or decreased mortality would appear to be associated with the interaction of three factors: age, maximum grip strength for both hand and right handgrip strength: a higher value of maximum handgrip for both hands (>305.500 N) and younger age (<69.641 years) are associated with decreased mortality, while lower values of maximum handgrip strength for

both hands, and of right handgrip in conjunction with old age (>70.968) are associated with increased mortality.

First, I compare the result of this research with the previous work of Ahamad and Bath [157, 158]. All the variables selected by CART in the best models are significant risk factors for increased or decreased 15-year mortality in unadjusted models. The CART exclusion of some previously identified factors may be explained by the fact that not only are they less important but also that Genetic Algorithms and Cox regression may select them only because of inner limitations of these techniques. In particular, with Genetic Algorithms the number of variables in the final model was decided a priori.

The selection of age as the initial splitting variable provides further evidence that this may be the most important factor affecting mortality in older people[142, 144, 147]. The selection of handgrip strength in the proposed models confirm its importance as predictor of mortality, that has been shown by other research [150-154]. The association of decreased handgrip strength with increased mortality was probably indicative of frailty[155].

The selection of the total prescribed medication confirms its association with mortality, showed by other study[156]

Refusing permission to access the OCPS file seems to be protective in reducing mortality risk: this is due to the fact that almost all people (19 out 20) who refused permission survived. I believed that this variable is not of interest.

5.5 Conclusion

I performed a CART analysis on risk factors previously identified using Genetic algorithms and Cox regression in order to predict long-term survival among older people. CART offers an opportunity to understand

the importance of the identified factors as predictors for mortality. The best model achieved a sensitivity of 76.3% and a specificity of 66.3%. The selection of variables are consistent with previous research [16,17]. In particular, age and handgrip strength are the most important variables associated with mortality in this study. Furthermore, and what is novel regarding this research is that I identified the pivotal values of the risk factor or of their combinations associated with increased or decreased mortality.

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