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Impact on clinical events and healthcare costs of adding telemedicine to multidisciplinary disease management programs for heart failure: results of a randomized controlled trial

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full propriety of the product. The use of this platform is financially supported by the National Health Service.

Abstract

Background

The role of telemedicine in the management of patients with chronic heart failure (HF) has not been fully elucidated. We hypothesized that multidisciplinary comprehensive HF care could achieve better results when it is delivered using telemedicine.

Methods and Results

In this study, 178 eligible patients with HF were randomized to either structured follow-up in the basis of face-to-face encounters (control group, 97 patients) or delivering healthcare using telemedicine (81 patients). Telemedicine included daily signs and symptoms telemonitoring and structured follow-up by the means of video or audio-conference. The primary end-point was non-fatal HF events after 6 months of follow-up. The median age of the patients was 77 years, 41% were female, and 25% were frail patients. The hazard ratio for the primary end-point was 0.35 (95% CI, 0.20-0.59; p-value<0.001) in favour of telemedicine. HF readmission (hazard ratio 0.39 [0.19-0.77); p-value=0.007]) and cardiovascular readmission (hazard ratio 0.43 [0.23-0.80]; p-value=0.008) were also reduced in the telemedicine group. Mortality was similar in both groups (telemedicine: 6.2% vs. control: 12.4%, p-value>0.05). The telemedicine group experienced a significant mean net reduction in direct hospital costs of 3,546 € per patient per 6 months of follow-up.

Conclusions

Among patients managed in the setting of a comprehensive HF program, the addition of telemedicine may result in better outcomes and reduction of costs.

Clinical Trial Registration: URL: http://www.ClinicalTrials.gov. Unique identifier: NCT01495078.

Key words: Outcomes Research, Heart Failure, Telemedicine, Disease Management, Chronic Care Model

Introduction

Randomized controlled trials (1) and recent pragmatic studies that have explored real-life implementations of HF management programs (2) have shown that organizing health care in accordance with the principles of the Chronic Care Model(3) improves adherence to prescription of evidence-based therapy and clinical outcomes.(1;2;4)

Much of the success of these programs is based, primarily, on delivering a planned, structured, nurse-based follow-up to patients and, secondly, on encouraging patient self-monitoring to promote early detection and treatment of decompensations in order to avoid readmissions and improve survival.(2;4)

In this regard, there has been a growing interest in implementing strategies for early detection of deterioration in these patients by taking advantage of telemedicine. Although this concept is very reasonable, well designed and adequately powered studies have failed to prove that a telemonitoring-based follow up strategy provides additional benefits to the usual care in chronic HF (CHF).(5;6)

These findings are in conflict with data coming from previous studies(7;8)showing that a telemedicine-based follow-up strategy was feasible and may be more efficient in reducing CHF-related clinical events compared to usual care. However, the efficacy of the combination of telemonitoring and comprehensive multidisciplinary care compared to comprehensive multidisciplinary care alone is a more controversial issue. In the Trans-European Network-Home-Care Management System (TEN-HMS) study(7), the primary end-point was not significantly different between remote structured follow-up with or without telemonitorizational though the combined strategy appeared to be marginally better in some secondary end-points. Moreover, in a recently reported trial conducted in Finland, the addition of telemonitoring to comprehensive management of HF did not improve clinical outcomes and was associated with an increase in the use of healthcare resources(9). Thus, In this regard, the exact role and the potential benefits (if any) of adding a combination of remote monitoring and teleintervention using telemedicine services on top of delivery of care within multidisciplinary HF programs needs further evaluation.

Thus, the aim of our study was to evaluate the impact of adding telemedicine to a multidisciplinary HF program.

Methods

The iCOR Trial (*insuficiència Cardíaca Optimització Remota* [heart failure remote optimization])was a single-center, randomized, open-label study designed to evaluate the efficacy of the addition of telemedicine (telemonitorization and teleintervention using videoconference) to an existing specialized, multidisciplinary, nurse-based, hospital-primary care integrated HF program for high-risk patients with CHF. The organizational characteristics of the program and the impact in health outcomes resulting from its implementation have been previously published.(2) In this study we aimed to compare the strategy of providing nurse-based structured follow-up to high-risk CHF patients through planned contacts between health care providers and patients and/or caregivers in the basis of face-to-face on-site encounters (usual care in our HF program) or provide the planned care using telemedicine with the combination of remote daily monitoring of signs and symptoms of HF (telemonitoring) and delivery of structured nurse-based follow-up health care using videoconference (teleintervention). The main hypothesis of this study was that adding telemedicine to an existing HF program would be associated with a reduction in the number of non-fatal HF events in high-risk patients with CHF. As secondary hypothesis we assumed that adding telemedicine would translate into a reduction in healthcare resource utilization and subsequent healthcare costs.

Study Design and Oversight

Patients were recruited during 23 months (December, 2010 to October, 2012) and followed for a fixed period of 6 months. The study protocol was approved by the institutional review board of the IMIM (*Hospital del Mar* Research Institute). All patients provided written informed consent. The study was registered on the website www.ClinicalTrials.gov (unique identifier: NCT01495078).

Study population, eligibility and recruitment

Inclusion criteria for this study were: over 18 years of age, clinical diagnosis of CHF according to the presence for >3 months of typical signs and symptoms of HF and the evidence of underlying structural heart disease, current hospital admission for acute decompensated HF needing intravenous diuretics. The study included patients with either reduced (HFrEF) or preserved (HFpEF) left ventricular ejection fraction (LVEF). HFpEF was defined as LVEF≥45%. Major exclusion criteria were moderate or severe cognitive impairment without a caregiver, lack of social support, institutionalized patients, life expectancy less than 1 year (excluding HF), planned end-of-life care,

planned cardiac invasive procesures, planned hemodialysis, death before hospital discharge and inability or unwillingness to give informed consent. Before discharge from the hospital and thus, before final inclusion in the protocol, patients had to be stable, without signs of fluid overload or low-cardiac output and receiving oral standard medication for CHF.

Randomization

Eligible patients that signed the informed consent were randomized in a 1:1 ratio to usual care (HF program or HFP) or intervention group (HFP+Telemedicine or HFP+T). Randomization was stratified according the presence or absence of fragility to ensure balanced assignment of frail patients to each group. This was achieved generating 2 different randomization lists with no specific permuted blocks: one for non-frail patients and one for frail patients. According to our HF program protocols, fragility was defined according to the following criteria: age≥90 years old or age 85-89 needing caregiver or moderate to severe dependency for basic activities of daily living (Barthel Index<90) at any age or moderate to severe cognitive impairment according to the Pfeiffer test at any age. Allocation of patients was performed and communicated to the investigators and attending healthcare professionals by independent administrative staff following the computer-generated randomization scheme.

Overview of the Home Tele-HealthCare Platform

The Home Tele-HealthCare (THC) Platform is a comprehensive solution for the care and monitoring of chronic patients, modelled and tested in patients with CHF that enables the provision of multichannel service and patient tracking through patient monitoring of biometric data (weight, heart rate and blood pressure), symptoms reporting (7 questions to capture worsening symptoms of the cardiac condition, mainly worsening heart failure, and 1 question to capture general worsening), generation and management of warning alarms (biometrics out of range) and alerts (information related to the function of the household devices). This was the gateway for receiving information from household devices using Bluetooth and sending patient's information to the clinical workstation using 3G technology. Both, home touch screen computer and 3G access were provided by the telemedicine service. In all cases, 3G connectivity allowed transmission of biometrics and performing videoconferences with good quality. In the current version, the patients' interface is

installed in a tablet with 3G connectivity provided by the telemedicine service. The platform allows promoting self-care and self-efficacy of patients by giving them up-to-date information about individual evolution of patient´s biometrics and issuing educational videos through this interface

The development of the telemedicine platform was conducted by telecommunication engineers of Telefonica Soluciones S.A in collaboration with researchers of the Hospital del Mar Medical Research Institute (IMIM) upon a Research and Innovation Agreement signed in between both institutions. The HTC platform is currently a commercial service of Telefonica Soluciones S.A. and this company owns full propriety of the product.

HF Programme with or without Telemedicine: differences between the two management strategies

The study was undertaken in an already existing specialized, comprehensive, multidisciplinary, nurse-based, hospital-primary care integrated heart failure programme for high-risk patients with CHF developed in an integrated health care area.(2) Patients assigned to the telemedicine group were followed and treated in the same manner as patients assigned to the HFP group in terms of number of scheduled visits and content of the intervention since both strategies shared the same protocols and algorithms. Each individual patient was contacted according to the assigned strategy: in the HFP group, the appointments were on-site face-to-face visits either at home (frail patients) or at the HF outpatient clinic (non-frail). In the HFP+T these encounters were virtual contacts by video-conference, audio-conference or telephone between the healthcare professional and the patient and caregiver (at home). All patients in the HFP+T performed daily automated telemonitoring of biometrics and symptoms using the Home THC Platform. Patients on this group were instructed to obtain bio-measures once a day, preferably after waking up, to be transferred to the clinical workstation. Telemedicine HF nurses reviewed alarms and alerts from the system everyday (working days and office hours). In the HFP group, as we mentioned, patients were instructed to perform these same determinations, record them and contact the nurse when these were out of range. In both strategies, in case of suspected decompensation, nurses could promote diuretic dose adjustments following specific protocols and algorithms and/or obtain the immediate support of a heart failure specialist. After hospital discharge, patients in the HFP+T group received an early home visit (<7 day) by the telemedicine HF nurse to set up the home telemedicine platform

and train patients and caregivers in its use. Similarly, patients in the HFP group received an early visit (<7 days) either at home (in frail patients by the primary care case manager) or at the HF outpatient clinic (in non-frail by a HF nurse). At the end of follow-up, continuity of care was provided by the primary care team including a case manager, primary care doctor and nurse and the primary care cardiologist.

Data collection

Medical history, relevant clinical and demographic information, physical examination, laboratory tests and functional evaluation was obtained at baseline. All patients underwent a complete psychosocial evaluation using validated questionnaires.(10-14) Self-efficacy (European Self-Care Behavior Scale)(13)and health-related quality of life (Minnesota Living with Heart Failure Questionnaire)(14) were also measured at the end of follow-up.

Follow-up and evaluation of end-points

All patients were evaluated at hospital discharge and for 6 months thereafter according to the above mentioned intervention strategies. Information on end-points was obtained from the hospital and primary care electronic medical records or by direct interview of patients or caregivers. The primary end-point and other secondary end-points including readmissions or death were adjudicated by an independent end-point committee whose members were unaware of group assignment.

Non-fatal heart failure event was the primary end-point of our study. This end-point has been used as component of the primary end-point in previous RCT(15). For the purpose of this study, non-fatal HF event was defined as a new episode of worsening of symptoms and signs consistent with acute decompensated HF requiring intravenous decongestive therapy (intravenous furosemide) according to the treating physician either on an outpatient basis (day-case HF hospital) or in the emergency department (<24 hours) or requiring unplanned hospital admission (>24 hours) or complicating the course of a non-HF hospital admission (i.e. bronchial infection).

Secondary end-points were all-cause and cardiovascular mortality, unplanned readmissions (all-cause, heart failure and cardiovascular), changes in patient-centred outcomes (self-efficacy and quality of life) and healthcare costs.

Methodology of Healthcare Costs Evaluation

The period of cost evaluation in each patient was comprised between the day post-discharge and the day of the end-of-study visit (end of planned follow-up or day of death). Cost calculation included pharmacy, complementary examinations, referrals, outpatient care, emergency room visits, readmissions and, procedures. The methodology of the EuroDRG (Diagnosis-Related Groups) project was used for the cost calculations. The hospital uses a cost accounting system based on full-costing allocation that allows for assessing direct costs derived from clinical activity. In the present study, cost estimation was based on a full-cost accounting system and on the criteria of clinical activity-based costing methods to obtain the highest sensitivity in the assessment of variability in clinical activity.

Moreover, this system ensures that the hospital's total costs are distributed among the patients. Allocation was based on directly assigning the cost of the following services to the patient: laboratory, pharmacy, radiology, nuclear medicine, pathology, and prosthetics. The information systems contain exhaustive data on human resources and their activity, i.e., storage, admissions planning, ambulatory and emergency care, operating rooms, diagnostic and complementary tests, and intrahospital consultations (specialist referrals). This information creates and automatically updates the cost drivers for overheads. This method has been used in health care cost evaluation by our group.(16)For this particular analysis, direct costs were also grouped in three categories: costs of hospitalization (cost of medical and nursing staff, pharmacy, invasive procedures, emergency room visits and associated costs that occurred during admissions), costs of diagnostics procedures (non-invasive diagnostic procedures including radiology, nuclear testing, laboratory, referrals to other specialists and associated costs) and ambulatory care (including costs of medical and nursing staff during ambulatory follow-up, use of the day-case hospital, treatments administered in the day-case hospital, the costs of the telemedicine service and associated costs of ambulatory care).

Statistical analyses

Demographic and other background data are summarized with basic descriptive statistics in the total cohort and according to the treatment group. For quantitative variables, the arithmetic mean (± standard deviation) or geometric means (95% confidence intervals) were calculated as appropriate, and P-values were derived from a two-sample t-test (non-parametric tests were used for skewed data). For qualitative variables, percentages were calculated and P-values were derived using χ^2 tests. Primary and secondary end-points were evaluated using Cox proportional-hazards model with group

assignment as the only covariate. We also conducted sensitivity analyses including 1) adjustment for relevant baseline covariates (age, gender, NYHA class, LVEF, NT-proBNP, criteria of fragility, educational level and baseline self-efficacy) and 2) including all patients that were screened and randomized. Unitary direct hospital costs obtained by hospital cost accountability methods were compared between treatment groups using non-parametric tests (Wald-Wolfowitz runs test and Kolmogorov-Smirnov z test for two independent samples). Changes in self-efficacy were analysed using Wilcoxon rank tests for paired variables. To evaluate accuracy of the analyses we undertook internal validation using re-sampling methods that included additional bootstrap analysis (1000cycles) of each bivariate and multivariate model.

All statistical tests and confidence intervals were constructed with a type I error (alpha) level of 5%, and P-values ≤ 0.05 were considered statistically significant. SPSSw version 18.0 (IBM, Armonk, NY, USA) was used for statistical analyses.

Results

Figure 1 reports the flow of patients in the process of screening. During the recruiting period of the study, 358 consecutive patients were screened. Of these, 133 were not eligible and 34 declined to participate. The remaining 188 patients were initially enrolled and randomized before discharge: 88 were assigned to the telemedicine group and 100 to the HFP group. At discharge, 7 patients in the HFP+T group and 3 patients in the HFP group did not fulfil eligibility criteria at the time of discharge and were finally excluded from the primary analysis. Thus the final study group consisted in 178 patients. Excluded patients, compared to those included, did not differ in terms of age, gender, LVEF, NYHA or pre-discharge NT-proBNP levels (all p-values>0.05).

Baseline Characteristics

Both groups were well balanced in terms of baseline demographic and clinical factors (table 1). There were no statistically significant differences between both arms in any of clinical of demographic variables evaluated at baseline. Median age of patients was 77 years (ranged from 40-92 years), and a high proportion of patients had HFpEF. The presence of comorbidities was high in this cohort of patients. There were no differences between both groups in terms of psychosocial characteristics (table 1) including self-efficacy and level of studies. One quarter of patients fulfilled

criteria of fragility and thus home-based care was planned for them. In these frail patients, 83% had a competent caregiver available (78% in the HFP+TM group vs. 87% in the HFP group, p-value>0.05). In the control group, care was delivered at home in the 25 patients that fulfilled fragility criteria (26%). In the remaining 72 patients of the control group, appointments were scheduled in our outpatient HF clinic. In the telemedicine group, 19 patients (24%) fulfilled fragility criteria and the remaining 62 patients of this group were not frail. In this latter group, all scheduled appointments were conducted using telemedicine. Quality of life assessed using the Minnesota Living with Heart failure Questionnaire was poor at baseline (median score of 55 points) and was not different between both groups (p-value>0.05). We prospectively evaluated how the patients would cope with the use of telecommunication technology as an instrument for their follow-up. At baseline, 61% of patients in the total cohort anticipated that they would have a high level of difficulty regarding the use of technological devices while 29% considered that this difficulty would be low. Despite this, the level of adherence to the use of the devices in the telemedicine group was very high with a proportion of missed biometric daily transmissions <1% of the planned and expected number of daily transmissions. Additionally, after 6 weeks of follow-up patients were asked to rate their level of satisfaction with the telemedicine system from 0 (not satisfied at all) to 10 (highest satisfaction). Regarding this, the mean score was 9.6±0.9 points, 79% rating 10 and 96% rating >7 points.

Primary Outcome

A total of 121 primary events occurred during the study period, 27 in the HFP+T group and 94 in the HFP group. In the telemedicine group, 2 non-fatal HF events were resolved in our HF-day case hospital, 5 were treated at the emergency department (<24 hours) and 15 required hospital admission. The remaining 5 non-fatal HF events occurred in the course of a non-HF hospitalization complicated with worsening HF. In the usual care group,31 non-fatal HF events were resolved in our HF-day case hospital, 12 were treated at the emergency department (<24 hours) and 40 required hospital admission. The remaining 11 non-fatal HF events occurred in the course of a non-HF hospitalization complicated with worsening HF. The mean number of non-fatal HF events was significantly lower in the HFP+T group compared to the HFP group (0.33±0.7 vs. 0.97±1.2, p-value<0.001, respectively). The primary end-point (figure 2, panel A) occurred at least once in 18

patients (22%) in the HFP+T group and in 51 (53%) of the HFP group (p-value<0.001). The rate of patients with multiple non-fatal heart failure events was also lower in the HFP+T group compared with the HFP group (p-value<0.001). The hazard ratio for the primary end-point (table 2, figure 2panel B) was 0.35 (95% CI, 0.20-0.59) in favour of the HFP+T group. In adjusted models the results were comparable with a hazard ratio of 0.33 (95% CI, 0.20-0.57, p-value<0.001). Inclusion of the patients that were screened and randomized but did not met final inclusion criteria (figure 1) showed similar results (p-value<0.001). According to an absolute risk reduction of 31% in the rate of the primary end-point, the number of patients necessary to treat (NNT) to prevent a non-fatal HF event would be 3.

Secondary Outcomes

All-cause readmission (table 3) occurred in 20 patients (25%) of the HFP+ T group and in 45 patients (46%) in the control group (p-value=0.003). The incidence per 100 patients-years at risk and the hazard ratio for this secondary end-point were also in favour of the group that received telemedicine (table 2). The positive effects in all-cause hospitalization obtained in the HFP+T group were mainly driven by the prevention of cardiovascular and particularly HF related-hospitalizations (table 2, table 3 and figure 3). In this regard, HF and cardiovascular readmission rate experienced a 19% and 20% absolute reduction respectively. Accordingly, the NNT to prevent one of these events would be 5 for both. In this direction, the mean number of days in hospital was significantly reduced in the HFP+T group for all cause, HF and cardiovascular readmissions (table 3). In those patients hospitalized, mean duration of each hospitalization tended to be shorter in the telemedicine group. In adjusted models, the results were similar (data not shown).

No significant differences were seen between the two groups with respect to mortality. All-cause death occurred in 5 patients (6.2%) in the HFP+T group and in 12 patients (12.4%) in the HFP group. As expected, deaths were mostly due to cardiovascular causes and occurred in 4 patients (4.9%) of the HFP+T group and in 10 patients (10.3%) in the HFP group. The combined end-point of all-cause death or HF-readmission occurred in 12 patients (15%) in the HFP+T and in 33 patients (34%) in the HFP group (NNT=5, p=0.003).

Patient-Centred Outcomes

Most surviving patients experienced an improvement in self-perceived health status: 113 patients (80%) out of the 142 surviving patients with available scores without imputation at the end of the

study reported an improvement > 5 points in the health-related quality of life questionnaire, considered to be the minimal clinically important change.(14)Such an improvement was reported in 63 patients (88%) in the telemedicine group and in 50 patients (71%) in the usual care group (p-value=0.02). Compared to baseline, self-efficacy evaluated with the European Self-Care Behaviour Scale improved in all patients (p-value<0.05 in both groups). Interestingly, the proportion of patients scoring 12 points (lowest score in this questionnaire indicating the best level of self-care) at the end of the study, tended to be higher in the HFP+T group compared to the HFP group (43% vs. 27%, respectively) although the difference was marginally non-significant (p-value= 0.055).

Subgroup Analyses

Subgroup analyses for the primary end-point (figure 4) showed consistent results across all pre-specified subgroups according to age, gender and other important clinical and psychosocial variables. The benefits were similar in patients with both HFrEF and HFpEF. Interestingly, there were no significant interactions between the main treatment effect and the presence of depressive symptoms, education level or the presence of fragility.

System-Centred Outcomes

Unitary direct hospital costs including the costs of implementing the telemedicine service were evaluated using our cost accounting system based on full-costing allocation. The total healthcare costs of the whole cohort were 1,124,245€. The costs of re-hospitalization accounted for two thirds (67%) of the total costs. The net savings in favour of the telemedicine group were 3,546 € per patient per 6 months of follow-up. The total healthcare cost experienced (figure 5-A) a relative reduction of 45% in the telemedicine group (p<0.001) when compared to the control group. This reduction was mainly driven by a significant reduction in costs of hospitalization (63% relative reduction, p<0.001) and a 59% relative reduction in diagnostic procedures (p=0.010) in the telemedicine group compared to the control group. On the other hand, ambulatory care costs in the telemedicine group increased two-fold compared to the control group. However, these costs only accounted for a 19% of the total costs. The reduction in costs observed in the telemedicine group was consistent across several subgroups of patients (figure 5-B).

Discussion

In our single-centre prospective randomized open blinded end-point study we found that follow-up of high risk patients with CHF in the setting of HF programs provides better results when planned care is provided using telemedicine. In particular, a telemedicine-based follow-up strategy was associated with a significant reduction in the number of non-fatal heart failure events (primary endpoint) and a reduced risk of HF and cardiovascular-related re-hospitalizations and associated number of days hospitalized. The benefits in the primary endpoint were consistent across all pre-specified subgroups. A non-significant trend toward a lower rate of all-cause and cardiovascular mortality was observed in the group that combined HFP and Telemedicine. Furthermore, a significant reduction of direct costs associated with hospital healthcare was observed in the telemedicine group compared to the usual care group.

These results are in line with the latest Cochrane review on this subject published in 2011(8) but are in contrast with the 2 largest published clinical trials.(5;6) Several differences between our study and other studies that may help explain the difference in results. First, in the Telemedical Interventional Monitoring in Heart Failure study (TIM-HF)(6)patients had to be stable and optimally treated for a pre-specified period of time before qualifying for inclusion. This probably resulted in a selection of patients at lower risk of events and thus, with less room for improvement. Thus, we may speculate that selection during hospitalization may allow early intervention in the most vulnerable patients at increased risk of readmission. In these, an early close monitoring may have a high added value. Second, despite our patients were anticipating a certain concern about the use of new technologies, the adherence and satisfaction during follow-up was high. This was possibly due to the simplicity of use of the telemedicine system, the active engagement of the primary care team and patients throughout the monitoring process and the proactive interaction of the HF team with patients and primary care teams. In the design of our telemedicine solution we involved telecommunication engineers, clinicians and patients. The aim was to develop a user-friendly communication tool conceived for elderly patients accordingly to the needs of real-world HF patients. Our patients transferred their biometrics and symptom status daily through an automated system. Thus, the high level of acceptance and adherence observed in our cohort are in contrast with the findings of the Telemonitoring to Improve Heart Failure Outcomes Study (Tele-HF)(5) where a centralized interactive voice response system was used to perform telemonitoring and where the adherence and involvement of patients was very low.

Other studies such as the TENS-HMS(7)included patients at high risk of readmission and reported a high level of adherence and satisfaction of patients with the telemonitoring system. In this study, remote structured follow-up either alone or in combination with telemonitoring were superior to usual care. However, the combination of telemonitoring and structured telephone support did no improve the primary outcome compared to structured telephone support alone although there was a marginal benefit in other secondary end-points. In our study, HF nurses were allowed to adjust the dose of diuretics when the biometry suggested a new decompensation. It is not clear whether a similar protocol was applied in the TENS-HMS. In fact, HF readmissions were higher in the combined group compared to structured telephone support alone although these hospitalizations tended to be shorter. The authors suggested that the early detection of new worsening in the patients allocated to home telemonitoring was translated into planned hospitalizations. The difference in the frequency of transmission of biometrics may also account for the differences observed in our study compared to the Finish study. Thus, differences in the protocols of nurse interventions and a lower frequency of telemonitoring may account for the divergence between our results and those observed in the TENS-HMS(7) study and the Finish(9) study respectively.

There are several reasons to support the role of remote monitoring in patients followed in a context of integrated management. Recent studies have shown that pulmonary and systemic congestion is associated to organ damage and that an early and more efficient decongestion may promote organ-protective effects particularly in the heart, kidney and liver.(17;18) According to this hypothesis, each new episode of congestion may promote a recurrent organ damage that in turn would further compromise the cardiac, renal and hepatic function. Thus, early detection and treatment of a new congestive event could help preserve the function of these organs.(17;18)This, in turn, may promote the prevention of future HF-related events or attenuate the severity of the new congestive episodes that could be easily managed with simple treatment intensifications. All these factors may prolong the periods of clinical stability required for treatment optimization. In favour of this hypothesis, we observed a reduction in the number of recurrent hospitalizations and a trend to a shorter hospital stay in the telemedicine group.

Our telemedicine service was deployed within a comprehensive, multidisciplinary, nurse-led, integrated hospital-primary care HF management program.(2) We embedded our telemedicine service in our integrated healthcare area to complement the existing local clinical pathways and

protocols in coordination with all the healthcare teams involved in the care of these patients, particularly with the primary care teams. Thus, our hypothesis is that the successful implementation of these systems requires a reorganization of healthcare at local level.(2;3)

The patient's interface of our telemedicine service incorporated elements such as feedback on biometrics and educational videos aimed to enhance self-efficacy and reassurance. From the perspective of patients and caregivers, these elements along with the support from the nurses may contribute to smooth the transition between hospitalization and the post-discharge period.(8)

These models of remote care have many advantages in the current healthcare context of aging and multiple comorbidities(19)allowing to extend a high standard care to patients who are often expelled from specialized care(8) Interestingly, in our study we have shown that the efficiency of telemedicine was independent from educational level, presence of HFpEF or HFrEF, severity of HF and the presence of depressive symptoms or frailty.

Study limitations

This study has the typical limitations of an open label trial where allocation to an intervention could not be masked. Our study was limited at 6 months. The optimal duration and the persistence of the observed benefit in such interventions are currently unknown. The telemedicine service was implemented within a comprehensive heart failure program. This means that the scalability and generalizability of the results is feasible if this telemedicine system is embedded in a well-organized process. An additional limitation of single center studies evaluating open label interventions is that motivation of the team may be at least partially responsible for achieving positive results that in turn may not be scalable to other centers or areas. To overcome this limitation, the two modalities of intervention performed in our study were delivered by two independent teams. Regarding this, we expected a similar degree of motivation and engagement in both intervention teams.

Conclusions

In this single-centre prospective randomized open blinded end-point study we have shown that the addition of telemedicine to an existing comprehensive heart failure program improves outcomes. Delivering healthcare to high-risk CHF patients with the combination of remote daily monitoring of signs and symptoms of HF (telemonitoring) and structured follow-up using videoconference (teleintervention) reduced the risk of non- fatal heart failure events and the risk of HF and

cardiovascular related readmissions compared to the strategy of providing structured follow-up on the basis of face-to-face encounters (usual care in a HF program). These benefits were seen across pre-specified subgroups of patients and were accompanied by reduction in hospital costs and improvement in patient-centred outcomes. Further research is warranted to evaluate generalization of the results, to explore the impact in mortality and to ascertain the optimal duration of this type of intervention.

Disclosures (Conflict of Interest)

The authors and the investigators involved in the design and conduct of the trial have no conflict of interests to disclose. The authors are solely responsible for the design and conduct of this study, study analyses, manuscript drafting and editing, and final manuscript contents

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Reference List

1. Roccaforte R, Demers C, Baldassarre F et al. Effectiveness of comprehensive disease management programmes in improving clinical outcomes in heart failure patients. A meta-analysis. *Eur J Heart Fail* 2005;7:1133-1144.

2. Comin-Colet J, Verdu-Rotellar JM, Vela E et al. Efficacy of an Integrated Hospital-primary Care Program for Heart Failure: A Population-based Analysis of 56 742 Patients. *Rev Esp Cardiol* 2014;67:283-293.

3. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA* 2002;288:1775-1779.

4. McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787-1847.

5. Chaudhry SI, Mattera JA, Curtis JP et al. Telemonitoring in patients with heart failure. *N Engl J Med* 2010;363:2301-2309.

6. Koehler F, Winkler S, Schieber M et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation* 2011;123:1873-1880.

7. Cleland JG, Louis AA, Rigby AS et al. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the Trans-European Network-Home-Care Management System (TEN-HMS) study. *J Am Coll Cardiol* 2005;45:1654-1664.

8. Inglis SC, Clark RA, McAlister FA et al. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: Abridged Cochrane Review. *Eur J Heart Fail* 2011;13:1028-1040.

9. Vuorinen AL, Leppanen J, Kaijanranta H et al. Use of home telemonitoring to support multidisciplinary care of heart failure patients in Finland: randomized controlled trial. *J Med Internet Res* 2014;16:e282.

10. Bellon JA, Delgado-Sanchez A, de Dios LJ et al. Patient psychosocial factors and primary care consultation: a cohort study. *Fam Pract* 2007;24:562-569.

11. Conde-Martel A, Hemmersbach-Miller M, Marchena-Gomez J et al. Five-year survival and prognostic factors in a cohort of hospitalized nonagenarians. *Eur J Intern Med* 2012;23:513-518.

12. De Craen AJ, Heeren TJ, Gussekloo J. Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old. *Int J Geriatr Psychiatry* 2003;18:63-66.

13. Gonzalez B, Lupon J, Domingo MD et al. Educational level and self-care behaviour in patients with heart failure before and after nurse educational intervention. *Eur J Cardiovasc Nurs* 2014;13:459-465.

14. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J* 1992;124:1017-1025.

15. Moss AJ, Hall WJ, Cannom DS et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-1338.

16. Benaiges D, Chillaron JJ, Carrera MJ et al. Efficacy of treatment for hyperglycemic crisis in elderly diabetic patients in a day hospital. *Clin Interv Aging* 2014;9:843-849.

17. Mentz RJ, Kjeldsen K, Rossi GP et al. Decongestion in acute heart failure. *Eur J Heart Fail* 2014;16:471-482.

18. Metra M, Cotter G, Davison BA et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J Am Coll Cardiol* 2013;61:196-206.

19. Sayago-Silva I, Garcia-Lopez F, Segovia-Cubero J. Epidemiology of heart failure in Spain over the last 20 years. *Rev Esp Cardiol* 2013;66:649-656.

Table 1. Demographics and baseline characteristics of the overall study population and according to treatment group

Variables	Total (n=178)	HF Program (n=97)	HF Program + Telemedicine (n=81)
Age, years	74± 11	75 ± 11	74 ± 11
Gender (female), No. (%)	73 (41)	38 (39)	35(43)
BMI, Kg/m^2	28 ± 5	28 ± 5	28 ± 6
Blood pressure, mmHg			
Systolic	121 ± 21	122 ± 18	121 ± 24
Diastolic	69 ± 13	67 ± 13	71 ± 14
Heart rate, bpm	74 ± 14	74 ± 14	73 ± 13
NYHA functional class, No. (%)			
I-II	96 (46)	57 (59)	39 (48)
III-IV	82 (54)	40 (41)	42 (52)
LVEF, No. (%)	47± 16	49 ± 16	45 ± 16
HFpPEF, No. (%)	102 (57)	58 (60)	44 (54)
Ischemic cause of HF, No. (%)	63 (35)	32 (33)	31 (38)

Comorbidities, No. (%)			
Hypertension	157 (88)	87 (90)	70 (86)
AFib	76 (43)	41 (43)	35 (44)
Diabetes Mellitus	86 (48)	49 (50)	37 (46)
CKD*	103 (58)	57 (59)	46 (57)
COPD	51 (29)	25 (26)	26 (32)
Iron Deficiency†	114 (64)	62 (64)	52 (64)
Anemia‡	92 (52)	52 (54)	40 (49)
Psychosocial Evaluation			
Self-efficacy**, points	22 ± 11	21 ± 10	22 ± 11
Educational level, No. (%)			
Illiterate	10 (6)	5 (5)	5 (6)
Elementary education	116 (65)	64 (66)	52 (64)
Middle school or higher education	52 (29)	28 (29)	24 (30)
Fragility, No. (%)	44 (25)	25 (26)	19 (24)
Treatment, No. (%)			
ACEI or ARBs	108 (61)	59 (61)	49 (61)
Betablockers	149 (84)	82 (84)	67 (83)

Aldosterone antagonists	47 (26)	24 (25)	23 (28)
Digoxin	23 (13)	14 (14)	9 (11)
Loop diuretics	174 (98)	93 (96)	81 (100)
Hydralazine-nitrate combination	48 (27)	27 (28)	21 (26)
Antiplatelet therapy/anticoagulant	152 (85)	81 (84)	71 (88)
Laboratory measurements			
Hemoglobin, g/dL	12.4 ± 2.5	12.2 ± 2.6	12.6 ± 2.3
eGFR-ml/min/1.73m^2	60 ± 26	58 ± 26	62 ± 27
NT-pro BNP, pg/mL	1585 (1349-1859)	1645 (1317-2054)	1514 (1196-1917)

Data are presented as arithmetic means ± SD (standard deviation) or numbers (with percentages) where appropriate. Data on NT-proBNP are presented as geometric means (95% confidence interval). COPD, chronic obstructive pulmonary disease. *CKD (chronic kidney disease) was defined as eGFR<60 mL/min/1.73m^2; †Iron deficiency was defined as ferritin<100 ng/mL or % transferrin saturation<20%; ‡Anemia was defined using the World Health Organization criteria (hemoglobin level < 12 g/dL in women and <13 g/dL in men). **Self-efficacy was evaluated using the European Self-Care Behaviour Scale (score range 12-60, with higher scores indicating worse self-efficacy);

Table 2. Clinical primary and secondary pre-specified endpoints according to treatment group.

	HF Program (n=97)			HF Program + Telemedicine (n=81)				
Primary Endpoint	Total Events	Patients with Event	Incidence per 100 patient-years at risk	Total Events	Patients with Event	Incidence per 100 patient-years at risk	*Hazard ratio (95% CI)	p-value
Non-fatal HF events	94	51	160.9	27	18	51.9	0.35 (0.20-0.59)	<0.001
Secondary Endpoints								
HF hospitalization	40	32	81.6	15	11	30.4	0.39 (0.19-0.77)	0.007
CV hospitalization	51	36	95.4	20	14	39.4	0.43 (0.23-0.80)	0.008
Non-CV hospitalization	25	16	37.0	10	9	24.6	0.76 (0.33-1.74)	0.509
All-cause hospitalization	78	45	126.4	30	20	59.3	0.50 (0.30-0.86)	0.011
All-cause death	12	12	25.6	5	5	12.9	0.68 (0.23-2.00)	0.485
CV death	10	10	21.3	4	4	10.3	0.70 (0.20-2.39)	0.570
All-cause death or non-fatal HF event	51	51	160.6	18	18	51.7	0.35 (0.20-0.59)	<0.001
All cause death of HF hospitalization	33	33	84.0	12	12	33.2	0.36 (0.19-0.71)	0.003

*Comparison of HF Program + Telemedicine vs. HF Program alone (reference category).

Table 3. Analysis of rate, number and duration of hospitalization according to treatment group during follow-up.

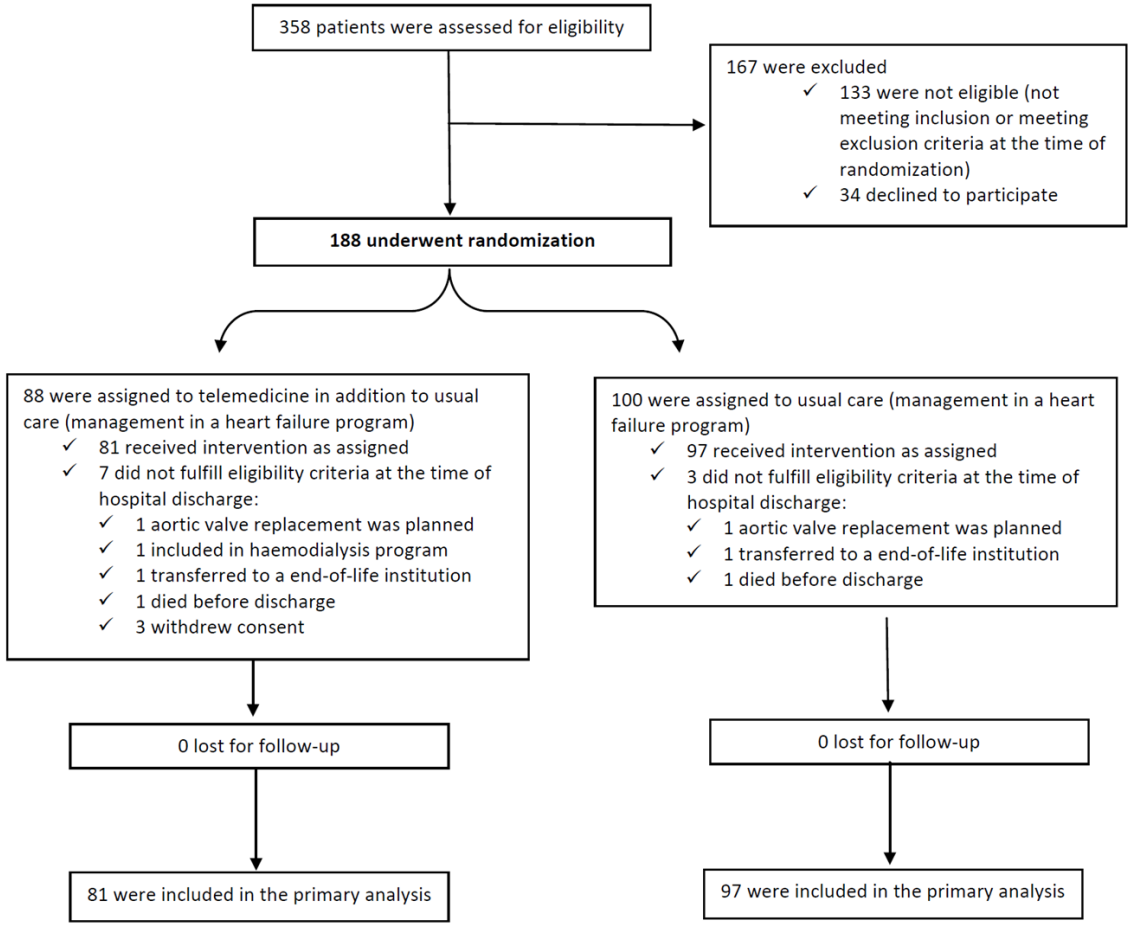
	HF Program (n=97)	HF Program + Telemedicine (n=81)	p-value
Heart Failure Hospitalization			
Rate, No. (%)	32 (33.0)	11 (13.6)	0.003
Number of readmissions,	0.4 ± 0.6	0.2 ± 0.5	0.004
Number of days in hospital*,	6.4 ± 12.6	2.2 ± 6.8	0.002
Mean hospital stay per admission (days)†	16.2 ± 14.0	12.3 ± 9.6	0.513
Cardiovascular Hospitalization			
Rate, No. (%)	36 (37.1)	14 (17.3)	0.004
Number of readmissions	0.5 ± 0.8	0.2 ± 0.6	0.004
Number of days in hospital*	7.2 ± 15.6	2.6 ± 7.2	0.002
Mean hospital stay per admission (days)†	14.0 ± 14.1	10.7 ± 9.1	0.604
Non-cardiovascular hospitalization			
Rate, No. (%)	16 (16.5)	9 (11)	0.388

Number of readmissions	0.3 ± 0.77	0.1 ± 0.4	0.261
Number of days in hospital*	4.7 ± 16.1	1.3 ± 4.5	0.178
Mean hospital stay per admission (days)†	18.2 ± 18.8	10.8 ± 8.3	0.427
All-cause hospitalization			
Rate, No. (%)	45 (46.4)	20 (24.7)	0.003
Number of readmissions	0.8 ± 1.2	0.4 ± 0.7	0.003
Number of days in hospital*	12.2 ± 22.5	4.2 ± 8.7	0.004
Mean hospital stay per admission (days)†	15.0 ± 12.8	12.3 ± 6.9	0.943

*mean number of days in hospital after the inclusion within each treatment group; †mean hospital stay in days only in admitted patients; Data are presented as means ± SD (standard deviation) or numbers (with percentages) where appropriate. Differences between treatment groups in continuous variables were evaluated using the U-Mann-Whitney Test for non-parametric data.

Figures

Figure 1. Flow chart of screening, randomization and follow-up of the study



patients.

Figure 2. Analysis of rate and risk of non-fatal heart failure events (primary end-point of the study) according to treatment group. Figure 2-A, Proportion of patients experiencing the primary end-point according to the treatment group allocation. Figure 2-B, Kaplan-Meier time-to-event estimates for the primary end point.

Figure 2_A

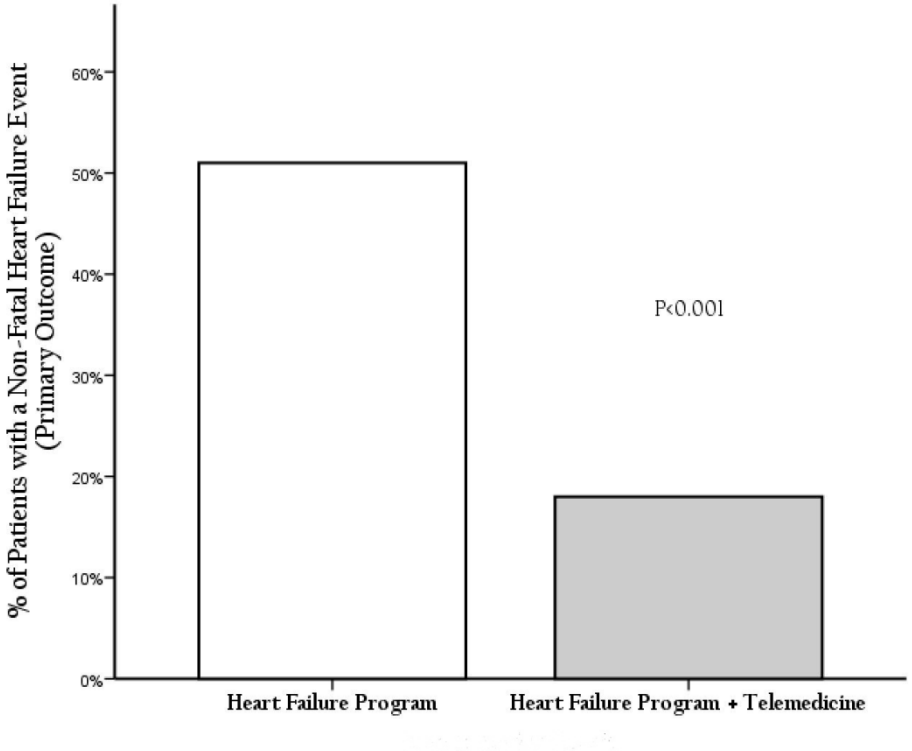
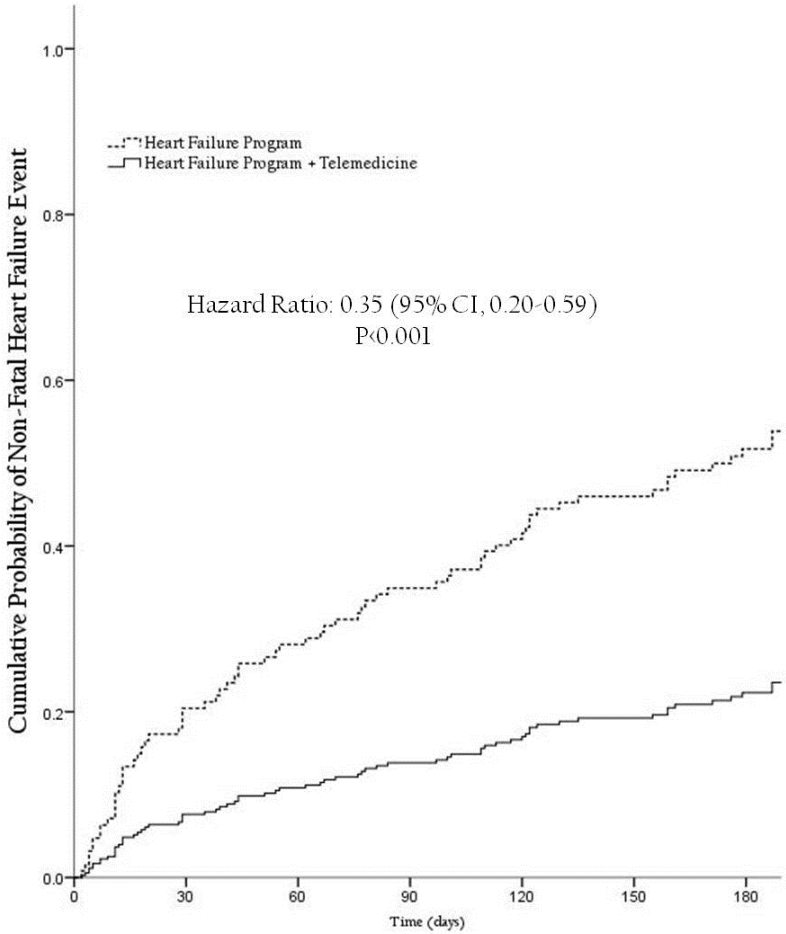


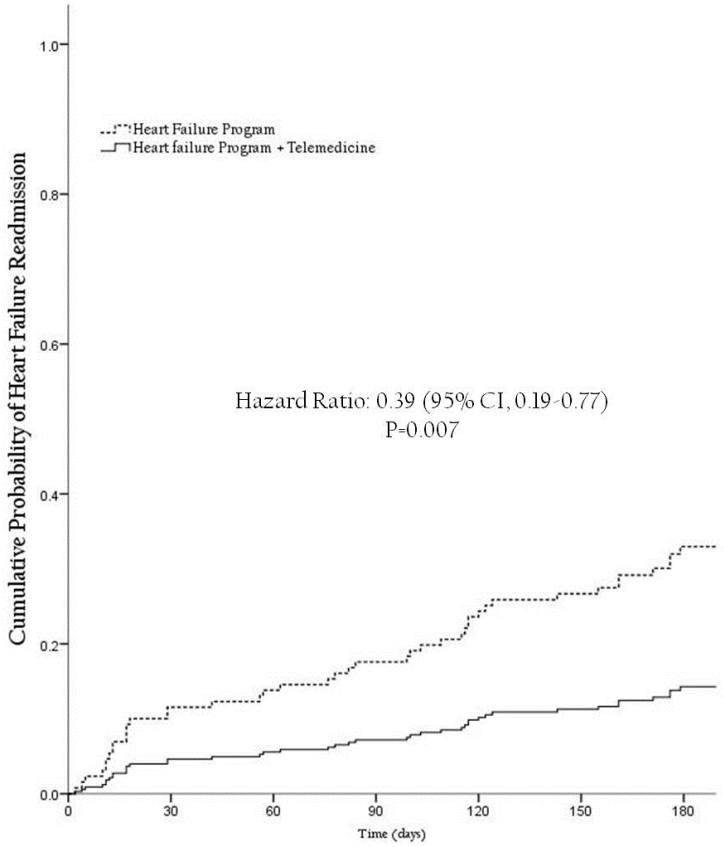
Figure 2-B



No.at Risk							
HF Program	97	77	70	62	56	45	18
HF Program + Telemedicine	81	75	72	71	65	56	25

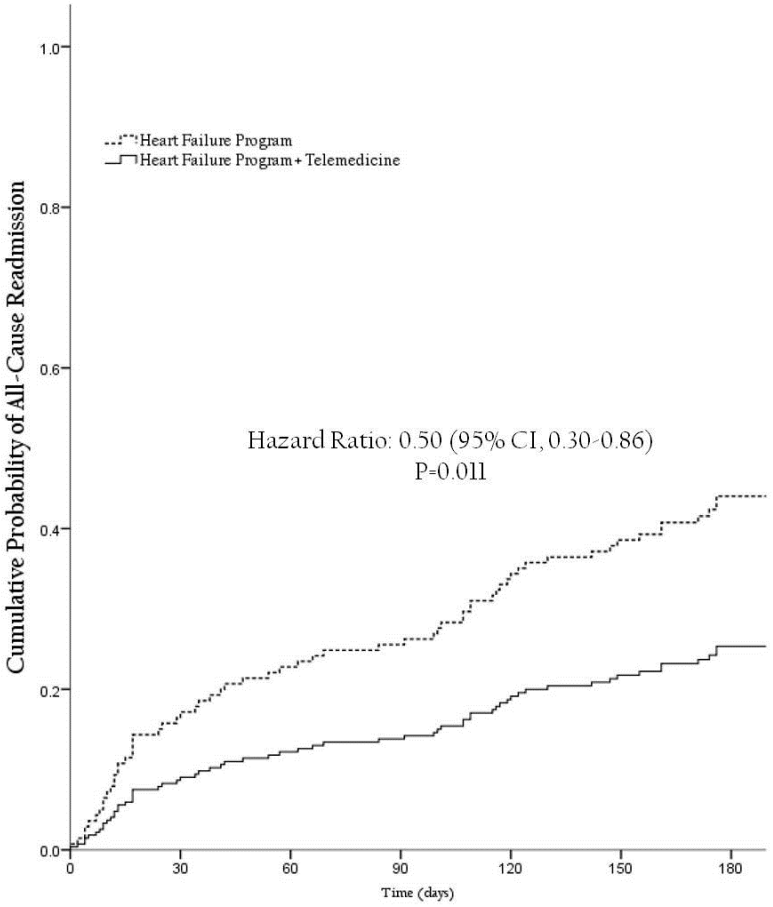
Figure 3. Kaplan-Meier time-to-event estimates for selected secondary end points (heart failure readmission, panel A; all-cause readmission, panel B), according to treatment group.

Panel A



No.at Risk							
HF Program	97	88	86	81	71	58	23
HF Program + Telemedicine	81	75	73	73	70	61	27

Panel B



No.at Risk							
HF Program	97	81	76	73	63	51	21
HF Program + Telemedicine	81	74	70	69	63	54	23

Figure 4. Subgroup analyses of the primary end-point of the study. HFP: Heart Failure Program; TM: Telemedicine; Ev: number of patients with event; Pat: total number of patients within each subgroup; HR (95% CI): Hazard Ratio with accompanying 95% confidence intervals; P-Int: P-value for the interaction. Depressive symptoms were defined using a cut-off point ≥ 4 in the 15-item Geriatric Depression Scale ; Inst. Dependency denotes ≥mild level of dependency for instrumental activities defined as a Lawton test score >8 points. HRQoL denotes health-related quality of life at baseline (impaired HRQoL was considered when the patient scored>55 points).

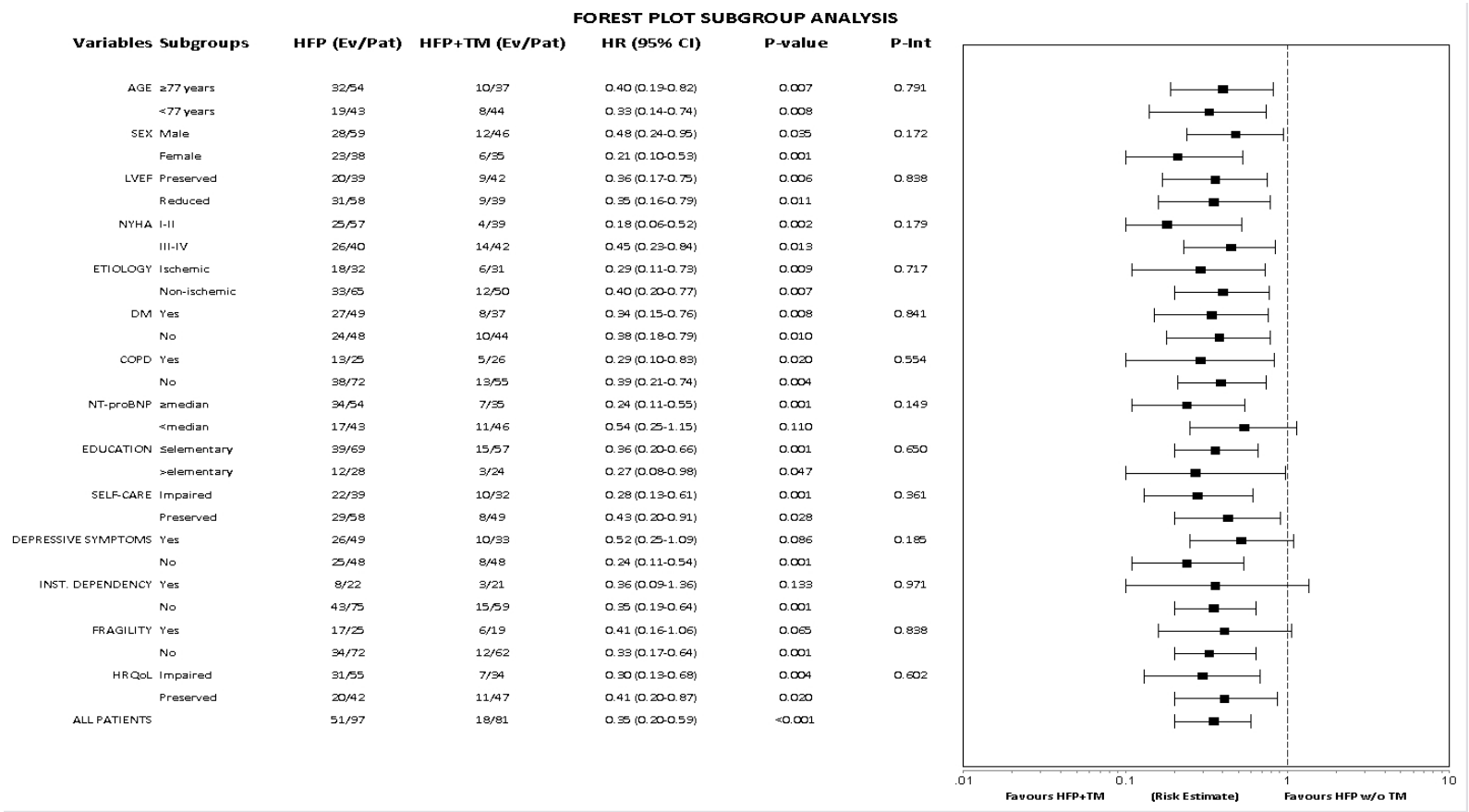


Figure 5. Analyses of global and unitary direct hospital healthcare costs expressed in euros (€). Figure 5-A represents the unitary costs per patient, expressed as mean value ±SEM according to the allocation group. Figure 5-B represents the relative reduction in total healthcare costs in selected subgroups of patients. "Primary school": subgroup of patients with primary studies. "Never used tech", denotes the subgroup of patients that never used any technological device except from telephone. "Problems with tech denotes" the subgroup of patients that would anticipate problems using technology for follow-up.

Figure 5-A

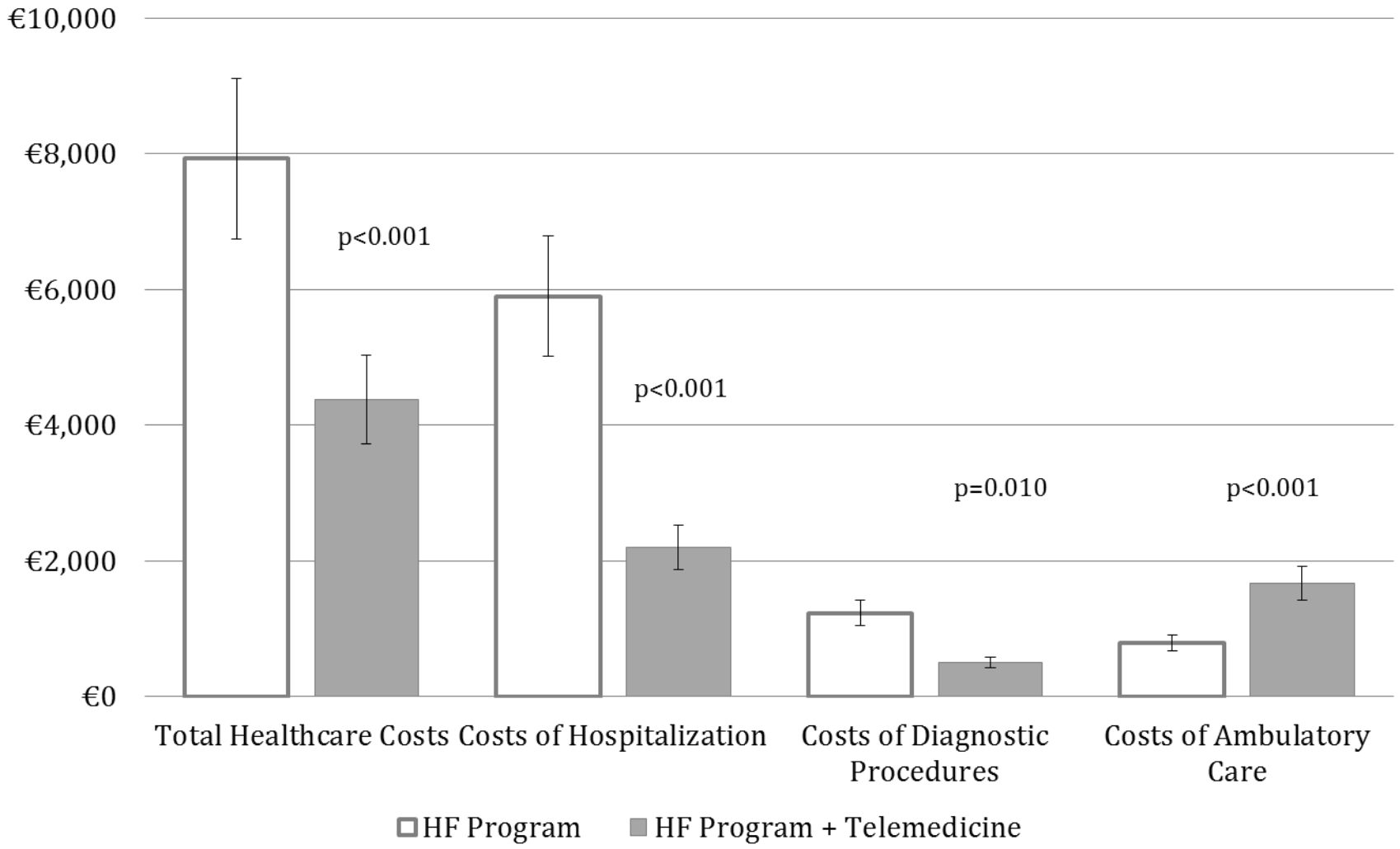
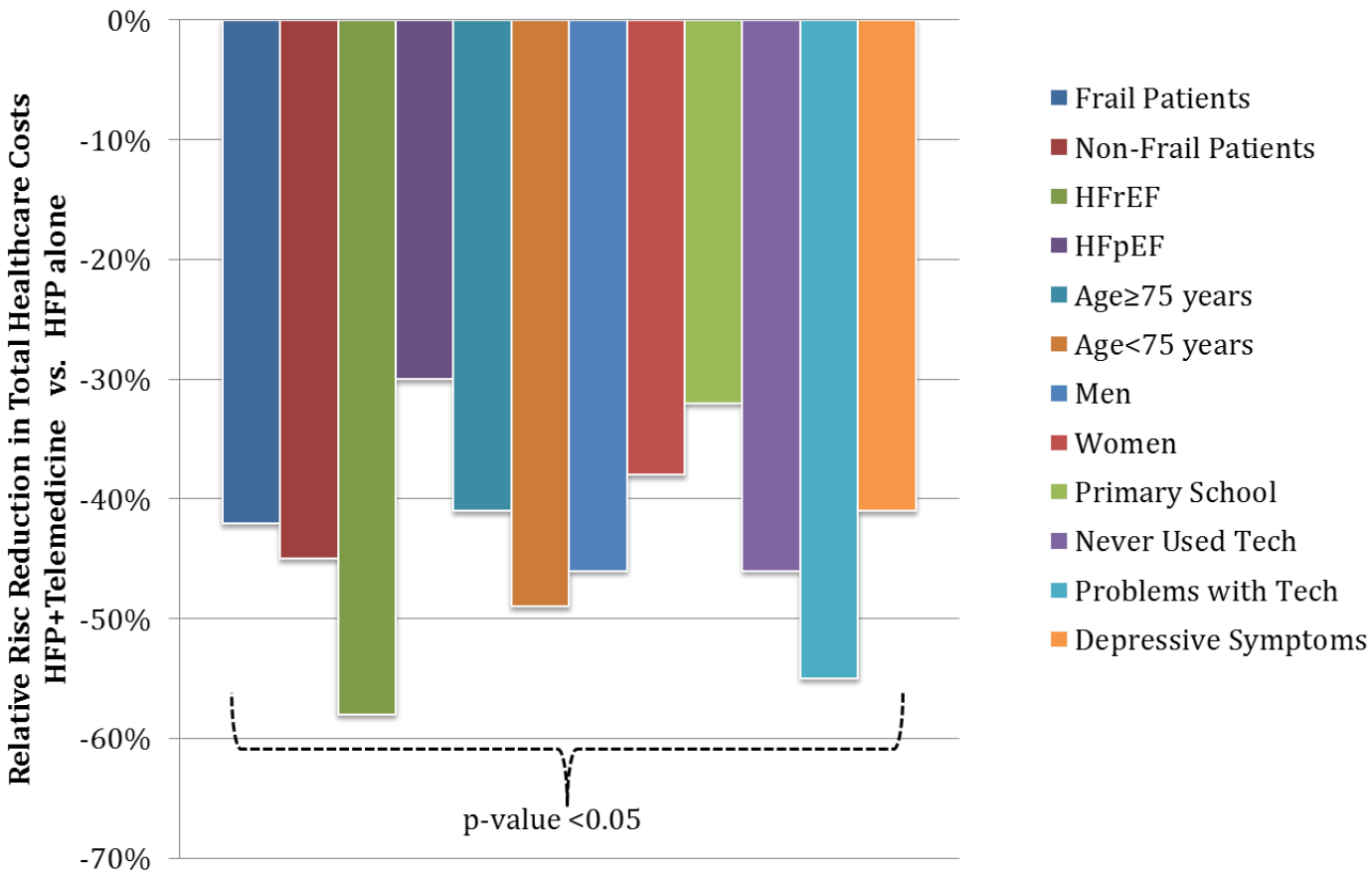

€10,000
€8,000
€6,000
€4,000
€2,000
€0
p<0.001
p<0.001
p=0.010
p<0.001
Total Healthcare Costs
Costs of Hospitalization
Costs of Diagnostic Procedures
Costs of Ambulatory Care
HF Program
HF Program + Telemedicine

Figure 5-B


Relative Risc Reduction in Total Healthcare Costs
HFP+Telemedicine vs. HFP alone
0%
-10%
-20%
-30%
-40%
-50%
-60%
-70%
p-value <0.05
Frail Patients
Non-Frail Patients
HFrEF
HFpEF
Age≥75 years
Age<75 years
Men
Women
Primary School
Never Used Tech
Problems with Tech
Depressive Symptoms