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ORIGINAL RESEARCH ARTICLE

Non-invasive telemonitoring improves outcomes in heart failure with reduced ejection fraction: a study in high-risk patients

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Abstract

Aims Non-invasive telemonitoring (TM) in patients with heart failure (HF) and reduced left ventricular ejection fraction (HFrEF) may be useful in the early diagnosis of HF decompensation, allowing therapeutic optimization and avoiding re-hospitalization. We describe a TM programme in this population and evaluate its effectiveness during a 12 month period.
Methods and results We conducted a single-centre study of patients discharged from hospital after decompensated HF, allocated into three groups: prospective TM programme, prospective HF protocol follow-up programme (PFP) with no TM facilities, and retrospective propensity-matched usual care (UC). TM effectiveness was assessed by all-cause hospitalizations and mortality; HF-related hospitalization (HFH), days lost to unplanned hospital admissions/death, functional capacity and quality of life (New York Heart Association, Kansas City Cardiomyopathy Questionnaire, 6 min walk test, and plasma N-terminal pro-brain natriuretic peptide) were also evaluated. A total of 125 patients were included [65.9 ± 11.9 years, 32% female, left ventricular ejection fraction 27% (21–32)]. TM was similar to PFP regarding effectiveness; TM reduced all-cause hospitalization and mortality (HR 0.27; 95% CI 0.11–0.71; $P < 0.01$) and HFH (HR 0.29; 95% CI 0.10–0.89; $P < 0.05$) as compared with UC. TM reduced the average number of days lost due to unplanned hospital admissions or all-cause death as compared with PFP (5.6 vs. 12.4 days, $P < 0.05$) and UC (5.6 vs. 48.8 days, $P < 0.01$). Impact on quality of life was similar between TM and PFP ($P = 0.36$).
Conclusions In patients with HFrEF and recent HF hospitalization, non-invasive TM reduced 12 month all-cause hospitalization/mortality and HFH as compared with usual care. TM also reduced the number of days lost due to unplanned hospital admission/death as compared with either an optimized protocol-based follow-up programme or usual care.

Keywords Telemonitoring; Non-invasive monitoring; Heart failure; Reduced ejection fraction

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This prospective study was performed at Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

Introduction

Heart failure (HF) affects 2% of the adult population.[1] Even though post-discharge programmes with multidisciplinary teams have proved to reduce all-cause re-hospitalizations and mortality and to be cost saving,[2–4] HF still contributes annually to all-cause mortality rates of 17% and to hospitalization rates of 44%.[5]

Driven by the development of new technologies, telemedicine is substantially growing,[6] allowing, among other things, the provision of patients' physiological parameters to health care professionals. It may represent a disruptive innovation

in the early diagnosis of HF decompensation and in the follow-up of chronic HF patients. Remote invasive monitoring has demonstrated to reduce the risk of recurrent HF hospitalization[7,8] with a favourable cost-effectiveness[9,10] profile, leading to its inclusion in the 2016 European Society of Cardiology guidelines as a class IIb recommendation, level of evidence B.[11] However, considering the non-invasive monitoring in HF patients, there is lack of data and conflicting results among studies.[11–15]

Most recently, the Telemedical Interventional Management in patients with heart failure (TIM-HF2) trial demonstrated that a structured remote patient management intervention, when used in a well-defined HF population, could reduce the percentage of days lost due to unplanned cardiovascular (CV) hospital admissions and all-cause mortality.[16] In the 2019 consensus document on clinical practice update on HF, a similar approach to the one used in TIM-HF2 may be considered to reduce the risk of recurrent CV and HF hospitalizations and the risk of CV death.[17]

However, real-world data on prognostic impact of non-invasive remote monitoring are very limited, and the best follow-up approach to manage these patients is yet to be established. We conducted a prospective study in a real-practice context to assess the feasibility and effectiveness of a telemonitoring (TM) programme in reducing hospitalization and mortality in a population with HF and reduced ejection fraction (HFrEF) considered at high risk for hospital readmission.

Methods

Study design and objectives

The study was prospective with a control retrospective group of patients hospitalized for acute (decompensated) HFrEF at the cardiology department of a tertiary hospital (Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal). Patients were included in the study after discharge from the cardiology ward. The groups were propensity matched.

The study was performed according to the principles outlined in the Declaration of Helsinki and the Good Clinical Practice guidelines of the European Commission. All patients provided written informed consent, and the study protocol was approved by the institutional ethics committee (Reference Number 389/17).

The main objective was to evaluate the effectiveness of a TM programme in the follow-up of patients with HFrEF. Effectiveness was quantified by a composite endpoint of all-cause mortality or all-cause hospitalization. Additional study objectives included evaluation of HF-related hospitalization, days lost due to unplanned hospital admissions or death, functional capacity, and quality of life. Functional capacity and quality of life were assessed on a 6 month basis according to the New York Heart Association (NYHA) classification, N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels, Kansas City Cardiomyopathy Questionnaire (KCCQ)[18] score, and 6 min walk test (6MWT).

Study population

We included adult male or female patients $\geq$ 18 years of age with HFrEF (EF $\leq$ 40%) who had at least one hospital admission due to HF decompensation in the previous 12 months.

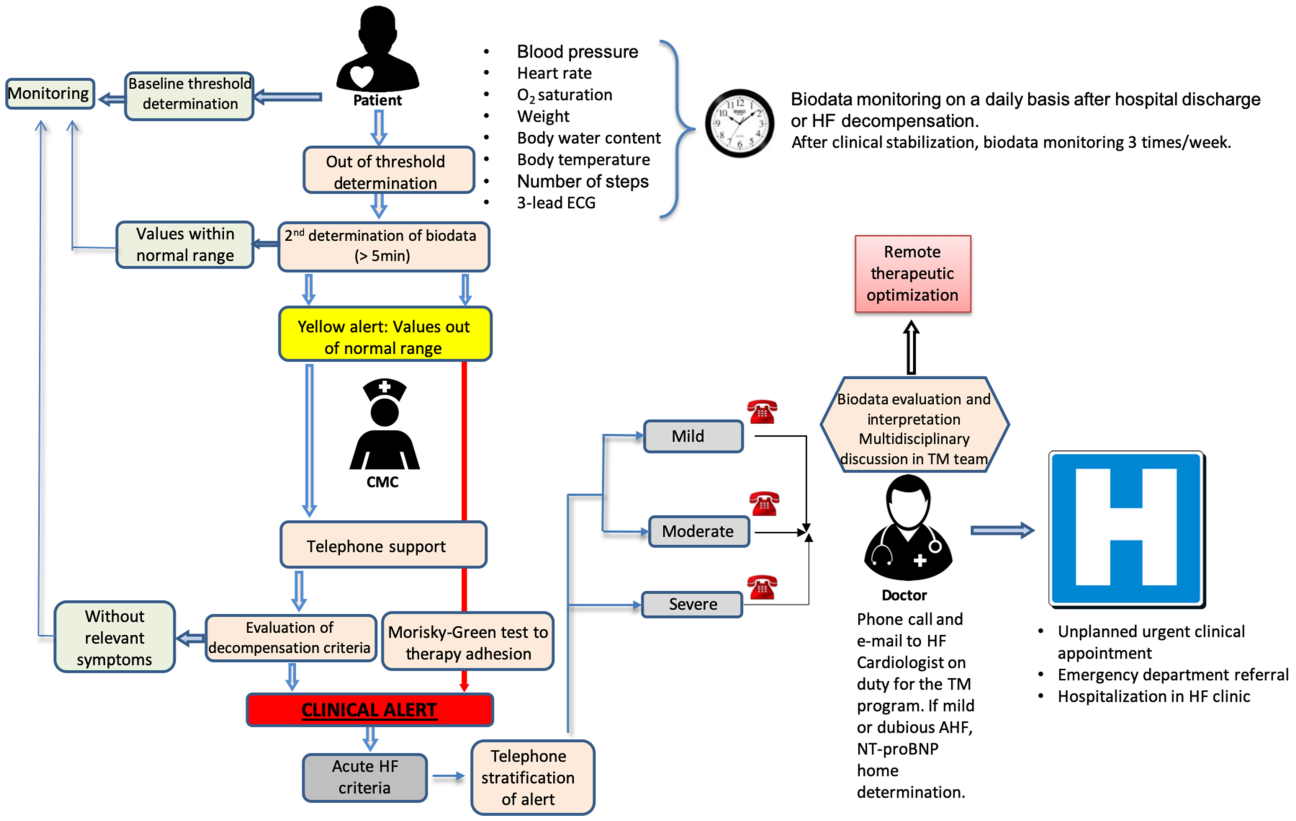
We excluded patients with cardiogenic shock in the previous 4 weeks, with heart surgery in the previous 8 weeks, on the waiting list for cardiac transplant, on haemodialysis, or that had psychiatric or cognitive impairments that constrained the understanding and utilization of telehealth devices.

After hospital discharge from the cardiology ward, three groups of patients were considered: (i) patients followed up prospectively with the support of non-invasive TM facilities (between December 2017 and December 2018); (ii) patients followed up prospectively accordingly to a protocol-based HF follow-up programme (PFP) but with no TM (between April 2016 and November 2017), and (iii) patients followed up according to the usual care practice (retrospective data), who were discharged before the implementation of the PFP or TM programmes (between April 2015 and April 2016). Patients were matched according to age, NYHA functional class at discharge, and left ventricular ejection fraction (LVEF).

Interventions

Patients assigned to the TM programme (TM group) were provided with home-monitoring devices to evaluate blood pressure, heart rate, peripheral oxygen saturation, body weight, total body water content, body temperature, daily walking steps, and three-lead electrocardiogram (ECG). *Figure* 1 illustrates the flowchart of the TM programme management. Further details are available in *Data S1*. Measurements were evaluated on a daily basis during the first week in the programme and after any acute event (e.g. hospitalization or visit to the emergency department for worsening HF). Otherwise, measurements were taken three times per week on alternate days. The ECG was performed once a week. A clinical monitoring centre (CMC), which included nurses, pharmacists, and cardiopneumology technicians, monitored the biodata. Biodata transmission was set at a fixed time, but patients were free to contact the CMC directly at any time (24/7) using the mobile phone provided for data transmission. At the beginning of the TM programme, the biodata baseline settings were defined for each patient, as well as the respective personalized alarm threshold. Whenever two or

FIGURE 1 Flowchart of the organization of the Telemonitoring programme.CMC, clinical monitoring centre; HF, heart failure.



more parameters were abnormal to any individual patient, an alert for a potential HF decompensation was triggered, CMC contacted the patient for more detailed information, and the adapted Portuguese version of the Morisky Medication Adherence Scale[19,20] was applied. When the alert was confirmed, the CMC contacted the cardiologist on duty for the TM programme reporting the altered biodata and patients' symptoms. According to the severity of HF decompensation, a personalized action was taken, which might include therapy optimization, at-home plasma NT-proBNP measurement, non-programmed medical appointment, or referral to the emergency department. In the absence of biodata measurement by the patient or difficulties in remote transmission of data, a technical alert was generated, and the CMC contacted the patient.

Patients included in the protocol-based follow-up programme (PFP group) had appointments at the hospital with the assistant cardiologist at the 7–10th day, 1st, 3rd, 6th, and 12th months after discharge (and additionally, whenever considered necessary) with clinical, laboratory, and ECG evaluations. Patient education and therapeutic optimization were pursued in accordance with European Society of Cardiology recommendations.[21]

Patients included in the usual care group (UC group) were followed up according to the assistant physician (cardiologist and/or GP) that included clinical, laboratory, ECG evaluation, and therapeutic optimization at physician's discretion.

Statistical analysis

Assuming that the estimated annual rate of all-cause mortality or all-cause hospitalization would be 65% in the control group (usual care) and 25% in the study group (TM) with an enrolment ratio of 2 (based on HF populational studies[5,22] and TM programme studies, TIM-HF,[13] respectively), it was estimated that 34 patients would need to be followed up in usual care and 17 in TM for 12 months to provide the study with a power of 80% to detect a significant relative reduction in the risk of all-cause mortality or all-cause hospitalization in the TM programme group, at an overall two-sided α level of 0.05.

Continuous variables were presented as mean ± standard deviation or median with interquartile range, as appropriate. Comparisons between patient groups were performed on continuous variables using the unpaired Student's *t*-test or Mann–Whitney test, as appropriate. Normality was assessed using the Kolmogorov–Smirnov test. Non-parametric Kruskal–Wallis test was performed to compare baseline characteristics between the three groups. Categorical variables

were compared using χ^2 tests. Paired comparisons at different time-points were performed using the Wilcoxon test.

Freedom from all-cause mortality or hospitalizations was evaluated with the Cox proportional hazards model and Kaplan–Meier analysis, with the hazard ratio and 95% confidence interval (CI) reported.

Days lost due to unplanned hospital admission or death were calculated as the number of days lost due to hospital emergency department visit (1 day was considered if hospitalization was not carried out) or the total number of days the patient stayed in-hospital divided by the intended follow-up of 365 days. For patients who died, the number of days lost between the date of death and the date of intended follow-up plus the number of days spent in hospital was counted.

For statistical tests, $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 23™.

Results

Population characteristics

In total, 125 patients with HFrEF were included: 25 patients assigned for non-invasive TM (TM group), 50 patients assigned for the protocol-based follow-up programme (PFP group) with no TM facilities, and 50 patients assigned for the usual care follow-up (UC group). From the initial 26 patients screened for the TM follow-up, one patient was excluded owing to difficulties in the management of non-invasive devices.

Overall, mean age of patients was 65.9 ± 11.9 years, and 32% were female. Idiopathic dilated cardiomyopathy was the main aetiology of HF, median LVEF at baseline was 27% (21–32), and mean NT-proBNP was 3085 ± 3228 pg/mL. There were no significant differences in the baseline clinical and laboratory characteristics of patients of the three groups (*Table* 1).

Table 1 Baseline characteristics of the study population

	TM group ($n = 25$)	PFP group ($n = 50$)	UC group ($n = 50$)	*P* value
Age (years), mean ± SD	65.4 ± 9.7	67.5 ± 11.0	64.58 ± 13.73	0.98
Female gender, *n* (%)	8 (32)	13 (26)	19 (38)	0.44
NYHA class, *n* (%)				
I	5 (20)	15 (30)	20 (41)	0.08
II	16 (64)	32 (64)	27 (55)	
III	4 (16)	3 (6)	3 (4)	
IV	0 (0)	0 (0)	0 (0)	
LVEF, median (IQR)	26 (21–30)	26.5 (19.8–34.3)	27.5 (21.8–31.3)	0.27
HF aetiology, n (%)				
Idiopathic DCM	14 (56)	26 (52)	23 (46)	0.90
Ischemic CMP	10 (40)	18 (36)	20 (40)	
Valvular CMP	1 (4)	4 (8)	5 (10)	
Other	0 (0)	2 (4)	2 (4)	
Laboratory data				
Serum creatinine (mg/dL)	1.23 ± 0.58	1.23 ± 0.45	1.32 ± 0.48	0.35
NT-proBNP, pg/mL	3112 ± 2456	3394 ± 4043	2959 ± 3097	0.50
Co-morbidities, n (%)				
Hypertension	17 (68)	36 (72)	35 (70)	0.94
Diabetes	9 (36)	19 (38)	28 (56)	0.12
Anaemia[a]	6 (24)	10 (20)	12 (24)	0.87
CKD[b]	12 (48)	23 (46)	27 (54)	0.95
CPD	8 (32)	20 (40)	22 (44)	0.66
Atrial fibrillation	8 (32)	27 (54)	25 (50)	0.19
Medical therapy, n (%)				
ACEi/ARB/ARNi	25 (100)	48 (96)	47 (94)	0.58
Beta-blocker	25 (100)	48 (96)	48 (96)	0.60
MRA	24 (96)	43 (86)	42 (84)	0.32
Diuretic	19 (76)	44 (88)	42 (84)	0.41
ICD	13 (52)	18 (36)	15 (30)	0.18
CRT	7 (28)	11 (22)	14 (28)	0.75

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CKD, chronic kidney disease; CMP, cardiomyopathy; CPD, chronic pulmonary disease; CRT, cardiac resynchronization therapy; DCM, idiopathic dilated cardiomyopathy; HF, heart failure; HTN, systemic arterial hypertension; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid-receptor antagonist; *n*, number; NYHA, New York Heart association functional class; PFP, protocol-based follow-up programme group; SD, standard deviation; TM, telemonitoring group; UC, usual care (UC) group.
[a]Haemoglobin < 12 g/dL (women) and <13 g/dL (men).
[b]Estimated glomerular filtration rate < 60 mL/min/1.73 m^2 (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula).

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Effectiveness

At 12 months, the composed outcome of all-cause mortality or all-cause hospitalization occurred in 5/25 patients (20%) in the TM group, in 17/50 patients (34%) in the protocol-based follow-up programme group, and in 28/50 patients (56%) in the usual care group (*Figure* 2).

There was no difference between TM and PFP groups regarding the effectiveness outcome (HR 0.54, $P = 0.2$). TM significantly reduced all-cause mortality or all-cause hospitalization when compared with UC (HR 0.27; 95% CI 0.11–0.71; $P < 0.01$), with a relative risk reduction of 73% and a number needed to treat to prevent one hospitalization or death of 3.

Hospitalization and mortality

There was no difference between TM and PFP regarding HF hospitalizations ($P = 0.4$). TM, when compared with the UC, significantly reduced the rate of HF-related hospitalization (12% vs. 36%, HR 0.29; 95% CI 0.10–0.89; $P < 0.05$) and all-cause hospitalizations (HR 0.29; 95% CI 0.11–0.75; $P < 0.001$).

Regarding all-cause mortality, one of 25 (4%) patients in the TM group, two of 50 (4%) patients in the PFP group, and eight of 50 (16%) in the UC group died, with no differences between groups.

Days lost due to unplanned hospital admission or death

Nine out of the 25 patients (36%) assigned for TM, 32 out of the 50 patients (64%) assigned for PFP, and 34 out of the 50 patients (68%) assigned for UC were admitted to hospital for an unplanned reason or died during the 12 month follow-up; 163 unplanned hospital admissions were reported, with a total of 3201 days lost to unplanned hospital admissions or death.

Patients in the TM group lost an average of 5.6 days per year compared with 12.4 days lost in the PFP group and 48.8 days in the UC group. There was a reduction in the average of days lost due to unplanned hospital admissions or all-cause death in the TM group compared with PFP group (5.6 vs. 12.4 days, $P < 0.05$) and compared with UC (5.6 vs. 48.8 days, $P < 0.01$; *Figure* 3). The percentage of days lost due to unplanned hospital admission or death per year was 1.5%, 3.4%, and 13.3%, respectively, for TM, PFP, and UC groups.

FIGURE 2 Effectiveness endpoint—cumulative all-cause hospitalization or all-cause mortality rate in telemonitoring (TM) group, usual care (UC) group, and protocol-based follow-up programme (PFP).

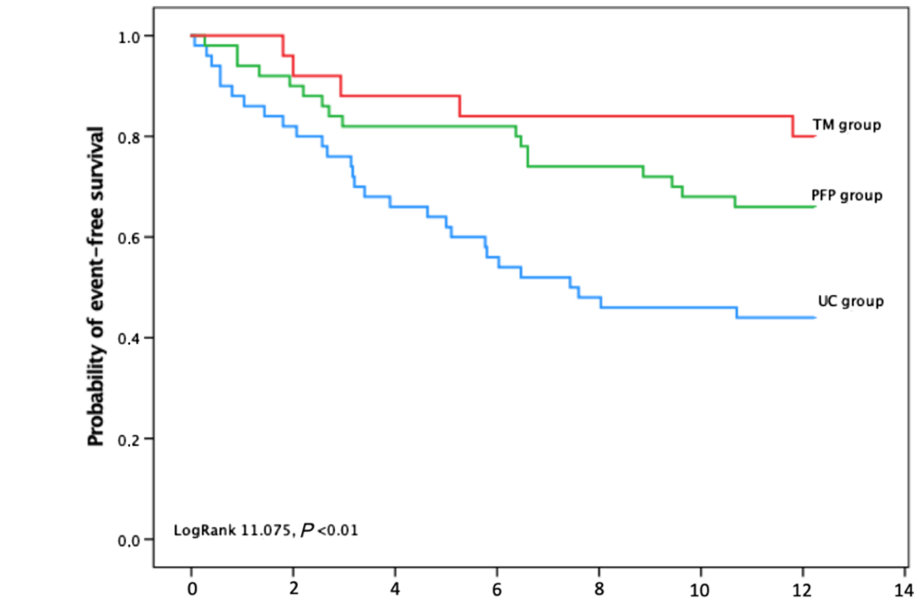

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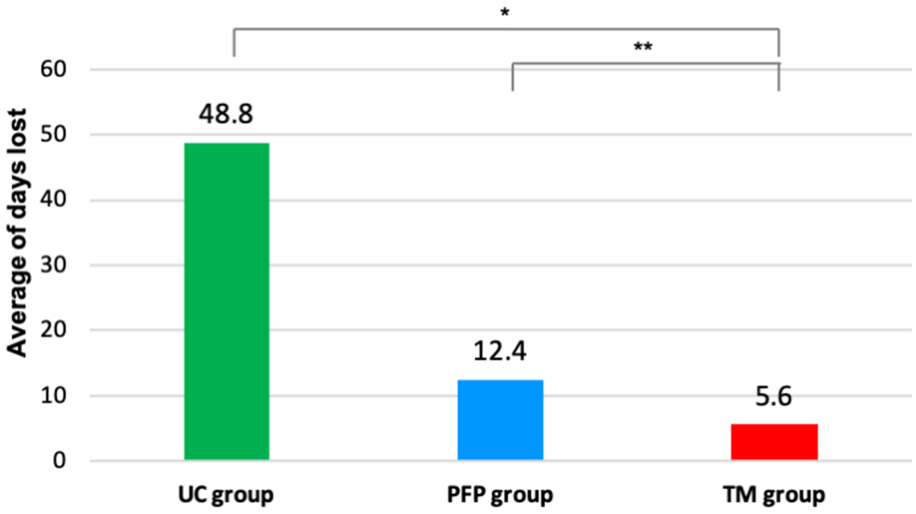
FIGURE 3 Number of days lost due to unplanned hospital admission or death during a 12 month follow-up. PFP, protocol-based follow-up programme; TM, telemonitoring group; UC, usual care group. * $P < 0.01$; ** $P < 0.05$.



Functional capacity and quality of life

At 12 months, TM group demonstrated a higher NYHA class improvement than PFP group (52.2% vs. 32%, $P < 0.05$) and UC group (52.2% vs. 16%, $P < 0.001$). Key outcomes on functional capacity and quality of life are presented in *Table* 2.

There was a significant reduction in the mean NT-proBNP plasma value during the 12 month follow-up both in the TM and PFP groups (from 3112 ± 2456 to 1655 ± 1670 pg/mL and from 3394 ± 4043 to 3183 ± 7170 pg/mL, respectively). In the UC group, there was a non-significant increase in NT-proBNP (from 2959 ± 3097 to 3009 ± 1241 pg/mL, $P = 0.60$).

The mean increase in total symptom score in the KCCQ (indicating fewer symptoms) for 12 months was similar in the TM and PFP groups (19.9 ± 26.2 vs. 13.5 ± 21.1, $P = 0.36$).

According to 6MWT results, patients in the TM group improved from an average of 316 m at baseline to 417 m at 12 months ($P < 0.001$).

Patient's compliance with telemonitoring

For patients assigned to the remote monitoring programme, at 12 months, 92% were compliant with the transfer of at least one parameter and 88% were at least 75% compliant with the transfer of all required data according to the protocol; 33641 vital parameters [median of 1293 per patient (120–1806)], with a total of 3168 alerts (1360 clinical alerts), were transmitted to the CMC during this period.

Discussion

In this study, we presented a modified method of follow-up of patients with chronic HFrEF at high risk for HF readmission, complementing the medical follow-up with technological facilities as non-invasive TM. This feasible model of non-invasive remote monitoring reduced all-cause

Table 2 Outcomes related to functional capacity and quality of life

Key secondary outcomes	TM group	PFP group	UC group
NYHA functional class			
Improvement, %	52.2	32	16
Unchanged, %	28	52	46
Worsened, %	19.8	16	38
Change in KCCQ total symptom score	19.9 ± 26.2	13.5 ± 21.1	NA
Change in NT-proBNP from baseline to 12 months of follow-up	−47% ($P = 0.014$)	−6.2% ($P = 0.019$)	1.7% ($P = 0.6$)
Change in 6MWT from baseline to 12 months of follow-up	31.8% ($P < 0.001$)	NA	NA

6MWT, 6 min walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not applicable (see text for details); NT-proBNP, N-terminal pro-brain natriuretic peptide.

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hospitalization/mortality (20% vs. 56%, $\underline{P} < 0.01$) and HF hospitalization (12% vs. 36%, $\underline{P} < 0.05$) compared with the usual care, during a 12 month period. It also reduced the number of days lost due to unplanned hospital admission or death compared either to usual care (5.6 vs. 48.8 days, $P = 0.001$) or to an optimized protocol-based follow-up programme (5.6 vs. 12.4 days, $\underline{P} < 0.05$).

TM programmes have shown controversial results due to the diverse methodologies employed and the heterogeneity of the HF populations included.[11,12,16] As congestion is the most frequent cause for HF decompensation,[23] monitoring of bio-signals may be important to detect it and optimize medical therapy, preventing hospital admission to the emergency department or even a hospitalization. Some of the major barriers in implementing TM with favourable results may include the target population and its compliance to the programme. TIM-HF2 study[16] included patients with at least one HF hospitalization in the 12 months preceding enrolment, and we hypothesized that this could have been one of the reasons why the programme reduced the percentage of days lost due to unplanned CV hospital admissions and all-cause mortality, as patients with recent hospitalizations from acute HF have a higher risk of decompensation in the vulnerable period.[24] In addition, TIM-HF2 study also excluded patients with major depression to strengthen adherence to the protocol. In fact, patient's compliance is a key point in any TM programme, because a low compliance may jeopardize the benefits of such monitoring, as it was observed in the TM in patients with Heart Failure trial (Tele HF[12]).

In the study presented herein, the benefits of TM were demonstrated compared with those of UC in HFrEF patients with a recent HF hospitalization and thus at a high risk of decompensation. Even though the effectiveness of TM was similar to PFP, it must be considered that patients on the PFP (all with optimized HF therapy) had at least five medical appointments in a 12 month period. Additionally, most patients benefited from a direct phone contact to his/her HF specialist in case of any potential decompensation, which may have smoothened the differences between TM and PFP. In fact, TM, when compared with PFP, reduced the number of days lost due to unplanned hospital admission or death. The impact of TM on this outcome demonstrates the importance of the programme in the reduction of emergency department visits, hospitalizations, and mortality. A longer time with no need for hospital care highlights the real-life impact of such programme in the quality of life of patients living with chronic HF.

On the other hand, compliance of patients to remote monitoring was fundamental to the positive results observed. At the beginning of the TM programme, data were undertaken on a daily basis implying a heavy burden on patients and caregivers. With that awareness, after 2 months from the start of the programme, we adapted the protocol to measure bio-signals daily during the first week in the programme or after any decompensation and only three times a week on alternate days thereafter, reducing the burden of monitoring that kept patients' adherence to the programme, with no significant differences in the outcomes. The frequent monitoring of biodata may have also improved patients' awareness regarding HF and improved their disease self-management. In fact, the high rate of patients' adherence may be a recognition of the impact of TM in their prognosis and quality of life.

Overall, the favourable prognostic impact of TM may come from the early diagnosis of a potential HF decompensation driving a prompt personalized treatment, within a well-structured workflow. The critical problem is not the accurately acquisition and transmission of biodata but the distinction between noise and true clinical alert. Artificial intelligence may potentially overcome this problem, helping in medical decisions in the future.[6]

Finally, with the increasing prevalence of HF and limited medical resources, TM may be an effective tool to decentralize patients from hospitals, whilst maintaining their remote follow-up, self-awareness of the disease, and patient–doctor empathetic relationship. The positive results observed in our study should be followed by a cost-effectiveness analysis.

Limitations

This was a prospective study with retrospective data regarding the matched UC group. Thus, retrospective data retrieval may have been limited to the registered medical reports.

The inclusion of patients throughout the years may have had an impact regarding treatment availability [e.g. angiotensin receptor-neprilysin inhibitor (ARNi)] or other non-controlled confounding factors. We believe the higher administration of ARNi in TM and PFP groups compared with UC group should be taken into consideration when evaluating our results, once we cannot exclude the impact of this confounding factor in our results.

We only included patients admitted in a cardiology ward due to HF decompensation, which may account for a selection bias of HF patients at higher risk for decompensation. Patients with HF admitted to internal medicine wards may have different profiles not evaluated in this study.

Only the first 25 patients were included in the analysis of this ongoing TM programme. However, it is important to emphasize this was a real-life study and that the selection of HF patients for this programme was planned to only target the population at higher risk of HF re-hospitalization and mortality.

The restricted 12 month follow-up of this study, similar to other studies,[11,12,16] may not evaluate the feasibility and effectiveness of TM in the long-term follow-up of HF patients. Thus, patients' compliance and motivation could be a problem in a longer-term follow-up. Additionally, stable patients

in TM for >12 months may not benefit the same from maintaining such rigorous and continuous monitoring. These long-term challenges should be further evaluated in real-life long-term TM programmes.

Conclusions

In patients with HF with reduced ejection fraction and a recent HF decompensation, remote non-invasive TM reduced 12 month all-cause hospitalization and mortality, as well as HF-related hospitalizations when compared with usual care. TM also reduced the number of days lost due to unplanned hospital admission or death when compared either with usual care or with an optimized protocol-based follow-up programme with no TM facilities.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Telemonitoring program in detail.

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