Evaluation of mobile health technology combining telemonitoring and teleintervention versus usual care in vulnerable-phase heart failure management (HERMeS): a multicentre, randomised controlled trial

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Summary

Background The potential of mobile health (mHealth) technology combining telemonitoring and teleintervention as a non-invasive intervention to reduce the risk of cardiovascular events in patients with heart failure during the early post-discharge period (ie, the vulnerable phase) has not been evaluated to our knowledge. We investigated the efficacy of incorporating mHealth into routine heart failure management in vulnerable-phase patients.

Methods The Heart Failure Events Reduction with Remote Monitoring and eHealth Support (HERMeS) trial was a 24-week, randomised, controlled, open-label with masked endpoint adjudication, phase 3 trial conducted in ten centres (hospitals [n=9] and a primary care service [n=1]) experienced in heart failure management in Spain. We enrolled adults (aged ≥18 years) with heart failure diagnosed according to the 2016 European Society of Cardiology criteria (then-current clinical practice guidelines at the initiation of the trial) who had recently been discharged (within the preceding 30 days of enrolment) from a hospital admission that was due to heart failure decompensation, or who were in the process of discharge planning. After discharge, participants were centrally randomly assigned (1:1) via a web-based system to mHealth, comprising telemonitoring and preplanned structured health-care follow-up via videoconference, or usual care according to each centre's heart failure care framework including a nurse-led educational programme. The primary outcome was a composite of the occurrence of cardiovascular death or worsening heart failure events during the 6-month follow-up period, assessed by time-to-first-event analysis in the full analysis set by the intention-to-treat principle. No prospective systematic collection of harms information was planned. The HERMeS trial is registered with ClinicalTrials.gov, NCT03663907, and is completed.

Findings From May 15, 2018, to April 4, 2022, 506 participants (207 [41%] women and 299 [59%] men) were randomly assigned: 255 to mHealth and 251 to usual care. The mean age of participants was 73 years (SD 13). Follow-up ended prematurely in 51 (20%) of 255 participants in the mHealth group and 36 (14%) of 251 in the usual care group. During follow-up in the mHealth group, cardiovascular death or a worsening heart failure event occurred in 43 (17%) of 255 participants, compared with 102 (41%) of 251 in the usual care group (hazard ratio for time to first event 0·35 [95% CI 0·24–0·50]; p<0·0001; relative risk reduction 65% [95% CI 50–76]). No spontaneously reported harms were reported in either group during follow-up.

Interpretation mHealth-based heart failure care combining teleintervention and telemonitoring reduced the risk of new fatal and non-fatal cardiovascular events compared with usual care in people with a recent hospital admission due to heart failure decompensation. The current findings could help to improve the care of patients with heart failure in the transitional post-discharge period by encouraging integration of mHealth into clinical practice guidelines.

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Introduction

Despite ongoing developments in the management of heart failure, such as new pharmacological approaches, implementation of specific heart failure programmes including specialised education strategies, or the digitalisation of medical care,[1,2] the condition remains a public health problem worldwide due to its high morbidity, mortality, impact on quality of life (QoL), and associated health-care costs.[3–5]

Worsening heart failure events, particularly when leading to hospitalisation admission, are a major cause of morbidity

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Research in context

Evidence before this study

We reviewed randomised and non-randomised studies and systematic reviews and meta-analyses evaluating electronic health (eHealth) delivered to people with heart failure by either non-invasive or invasive strategies, published up to Sept 30, 2023. We did a search of PubMed using the terms "heart failure", "eHealth", "mHealth", "telemedicine", and "telemonitoring", restricted to articles published in English. Regarding the benefits of remote monitoring in patients with heart failure, several studies have shown mixed results. Recent evidence has shown the effectiveness of invasive technologies (eg, cardiac implantable devices and invasive haemodynamic monitoring) in improving clinical outcomes in heart failure. However, these invasive technologies are not easily applicable to most people with heart failure given the costs and logistical and financial challenges for real-world patients with heart failure. In the past 20 years, there has been increasing interest in the development of non-invasive, inexpensive strategies aimed at global or population-based heart failure management, which offer a strong safety profile and high capacity for adaptation and integration into different models of heart failure care. However, evidence is scarce on the usefulness of non-invasive technology in the monitoring and care of patients with heart failure. The 2021 European Society of Cardiology heart failure guidelines only offer grade IIb recommendations (per the American Heart Association evidence grading system) with level B evidence for both invasive and non-invasive strategies. Barriers to implementation include factors related to health-care systems, health-care professionals, and the patients themselves (eg, in terms of patient literacy, information and communication technologies skills, or willingness towards this paradigm change in care). Additionally, there has been a paucity of assessment of mobile health (mHealth) solutions in clinical trials. Thus, the Heart Failure Events Reduction with Remote Monitoring and eHealth Support (HERMeS) clinical trial sought to establish the role of non-invasive digital solutions, specifically mHealth, in the follow-up of patients in the transitional period following discharge from a hospital admission due to heart failure.

Added value of this study

To our knowledge, HERMeS is the first trial to integrate and assess an mHealth-based intervention combining telemonitoring and structured teleintervention via videoconference in early post-discharge patients with heart failure, as a period of high vulnerability to new clinical events. The trial assessed real-world individuals in multiple health-care settings (from specialised hospital care to homecare settings). Results showed that the integration of mHealth into day-to-day heart failure monitoring with user-friendly technology that provided the possibility of direct contact with a health-care team in the early post-discharge period contributed to a significant reduction in cardiovascular deaths and worsening heart failure events, among other clinical events, over 6 months of follow-up. The effect of mHealth appeared to be achieved via early identification of the signs and symptoms of worsening heart failure, allowing rapid optimisation of the care of vulnerable patients, including self-care and adjustment of heart failure treatments, to mitigate episodes of worsening heart failure.

Implications of all the available evidence

The results of the HERMeS trial indicate that, first, mHealth is a user-friendly tool as shown by high patient adherence and satisfaction, which can help health-care teams, caregivers, and patients themselves manage heart failure reactively, with optimisation of drug therapy, to quickly avoid heart failure events and thereby reduce the risk of worsening episodes in the vulnerable post-discharge period. Second, in the context of previous trials (ie, BEAT-HF and iCOR), the combination of telemonitoring and teleintervention appeared to be key to the success of mHealth to enable rapid medical intervention to halt developing heart failure events. Third, patient populations with a high vulnerability to new clinical events (eg, after hospital admission for heart failure decompensation) are likely to experience high clinical impact from mHealth-based monitoring strategies. And finally, it could be a useful tool for most patient profiles and heart failure care settings in which monitoring is performed, subject to adequate care team staffing and training. Achieving guideline-directed medical treatment and avoiding or terminating decompensation events early via mHealth might help to reduce the health, humanistic, and economic burden of heart failure in ambulatory patients during the vulnerable post-discharge phase. The current findings could help to improve the care of patients with heart failure in the transitional post-discharge period by promoting the integration of mHealth-based solutions into new heart failure clinical practice guidelines with more robust recommendations on its use.

and mortality, as well as health-care burden and poor QoL. Transitional care models for heart failure focus on the periods when patients are most likely to have new adverse clinical events, in particular the early post-discharge period following hospitalisation, also referred to as the vulnerable phase.[6,7] Electronic health (eHealth) solutions have emerged as innovative strategies in transitions of care to improve patient outcomes, especially in the early post-discharge period.[8] Both invasive (eg, cardiac implantable devices and invasive haemodynamic monitoring) and non-invasive telemonitoring approaches have been shown to have varying amounts of effect on outcomes.[9,10] Potential non-invasive solutions include structured telephone follow-up,[11] remote home-based telemonitoring and teleintervention,[12–19] and wearable devices.[20]

To date, most studies have assessed telemonitoring and teleintervention strategies individually[12,13] and predominantly in patients with stable heart failure.[15,16] The potential for synergistic effects of combining non-invasive telemonitoring and structured teleintervention with mobile health technology (mHealth) has only been explored in a single-centre pilot trial published in 2016, which showed

promising results.[17] However, its efficacy in well designed, multicentre randomised trials in a broad range of patients, including older patients with increased frailty or functional dependency, among other criteria, recently admitted to hospital due to heart failure (ie, the post-discharge vulnerable phase), when the greatest benefit might be achieved, has not been tested.

Therefore, we designed the Heart Failure Events Reduction with Remote Monitoring and eHealth Support (HERMeS) trial to assess the efficacy of a non-invasive telemedicine service based on mHealth on clinical outcomes.[21] The trial compared structured telemonitoring combined with videoconferencing (teleintervention) with usual care based on face-to-face on-site visits in patients with heart failure during the vulnerable post-discharge phase.

Methods

Study design

The HERMeS trial was a 24-week, randomised, controlled, open-label, masked endpoint adjudication, phase 3 trial conducted in ten centres (hospitals [n=9] and a primary care service [case management; n=1]) experienced in heart failure management in Spain (appendix 1 p 9). The trial was designed and implemented by the HERMeS Steering Committee in accordance with the principles of the Declaration of Helsinki (1996), the International Conference on Harmonization Good Clinical Practice guidelines, and local, national, and international regulations, including legal regulations about personal data confidentiality (Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantee of Digital Rights of the Spanish Parliament and, by extension, EU General Data Protection Regulation [EU] 2016/679). The HERMeS study protocol was evaluated by the Spanish Agency of Medicines and Medical Products (Madrid, Spain), which classified it as a non-observational study without drugs, and it was approved by the institutional review boards of the coordinating centre (Bellvitge Biomedical Research Institute [IDIBELL], Barcelona, Spain; reference number IDIBELL-2017/PR190/17) and recruiting centres. Both the Steering Committee and the authors (SY, JC-C and CE) who had access to the raw data ensured its completeness and accuracy. In addition, these individuals assured that the trial was done in accordance with the protocol. CONSORT reporting guidelines for randomised trials of non-pharmacological treatments were used for this paper (appendix 1 pp 24–37).[22] The trial is registered with ClinicalTrials.gov, NCT03663907. The study protocol is provided in appendix 2.

Participants

Individuals were eligible for enrolment if they were adults (aged ≥18 years) with heart failure diagnosed according to the then-current European Society of Cardiology criteria (published in 2016)[23] who had recently been discharged (within the preceding 30 days of enrolment; ie, vulnerable-phase patients) from a hospital admission that was due to heart failure decompensation, or who were in the process of discharge planning. The trial design aimed to encompass real-world patients, regardless of heart failure classification according to left ventricular ejection fraction (LVEF)[1] and independent of the health-care setting in which the condition was managed (multidisciplinary heart failure units, cardiology units, internal medicine units, and patients with home-based follow-up by primary care [case management] due to functional dependency, comorbidity, and social status, among other medical criteria). Patients with moderate or severe cognitive impairment (ie, dementia with noticeable declines in function, the need for some assistance with the activities of daily living, and impaired memory) without a competent caregiver (competency per investigator's discretion; where caregiver was defined as an individual who provides assistance and support to another person who is unable to fully care for themselves due to age, illness, disability, or other health-related conditions), patients without social support per the investigator's discretion, or institutionalised patients, among other criteria, were excluded. Detailed inclusion and exclusion criteria have been published previously.[21] Beyond the inclusion and exclusion criteria, there was no rigorous prespecified protocol for pre-screening to identify individuals who were suitable for enrolment. All consecutive patients meeting the heart failure diagnosis and recent hospital admission criteria were screened for eligibility and offered participation if they fulfilled all selection criteria. All enrolled participants provided written informed consent.

Randomisation and masking

Eligible patients before discharge or attending outpatient clinics within a period of 30 days from discharge, who agreed to participate and signed the corresponding written informed consent, were formally enrolled. Randomisation was performed after the patient was discharged. The randomisation process was implemented centrally via a dedicated algorithm on the Research Electronic Data Capture (REDCap; version 14.05.16) platform. The principal investigator at each centre could access REDCap via its own Internet Protocol address to allocate individuals to study groups via the centralised algorithm. These principal investigators could, depending on their role in each of the teams, be involved in the care and treatment of the patients included in the trial. The algorithm and allocation table on REDCap were provided by the Biostatistical Service of IDIBELL; the Biostatistical Service also monitored and maintained the electronic case report forms in REDCap, with no further involvement in the trial. Participants were randomly assigned (1:1) to structured follow-up based on face-to-face appointments (usual care group) or to health care delivered by mHealth (mHealth group). Randomisation was stratified at each centre and according to the presence or absence of frailty to ensure balanced assignment of frail individuals to each group. The randomisation procedure and frailty criteria have been published previously,[21] with frailty defined in accordance with the

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For **REDCap** see https://redcap.idibell.cat/redcap_v14.0.16/index.php?pid=347

See **Online** for appendix 1

See **Online** for appendix 2

definition used in the iCOR randomised trial.[17] All participants and the treatment team were aware of treatment assignment after randomisation.

A clinical endpoint committee (PM, FF, Jd-JB, and IZ-R) who were masked to study group assignment adjudicated all clinical events that occurred during the study. All statistical analyses were done by a masked statistician independent of the research team and, therefore, not involved in the process of patient selection and recruitment, or in the follow-up and care of the patients.

Procedures

Detailed information regarding the mHealth-based follow-up as well as the schedule of planned visits and monitoring in the two treatment groups has been previously reported[21] and an overview is provided in appendix 1 (pp 2–3). Clinical events were prospectively captured by local investigators and reported through a dedicated electronic case report form. All the participants included in the study were followed up for 24 weeks (6 months) for the collection of outcome data. During this period, harms could be reported reactively via the Spanish Pharmacovigilance System for Medicinal Products for Human Use, but per agreement with the Spanish Medicine Agency there was no routine, planned collection of data related to safety or adverse events. Information on participant demographic and clinical characteristics including self-reported gender (male or female) was collected at the baseline study visit. No data on ethnicity or race were collected.

For the **Spanish Pharmacovigilance System** see https://www.notificaRAM.es

At each centre, the health-care team providing care was also responsible for implementing the trial protocol, including the delivery of mHealth. This approach was taken to ensure that mHealth was applied in a real-world setting. All participating centres were required to provide a high standard of heart failure care according to the available European Society of Cardiology guidelines at the time of the study (2016 and 2021).[1,23] The heart failure care teams were mainly comprised of heart failure specialists and nurses specialised in the care of patients with heart failure (appendix 1 p 3) and were present during a standard working day as defined for each centre.

Usual care was provided according to each centre's heart failure care framework and according to a prespecified baseline level of care, which comprised a nurse-led educational programme to encourage daily biomedical data monitoring (eg, blood pressure, heart rate, and weight) and symptoms, and encouragement to promptly inform their health-care team when alarming biomedical values were detected. Because all the recruiting centres had active and mature ongoing heart failure programmes, there was no maximum number of pre-planned contacts; only a minimum number of planned contacts (four) were recommended in the usual care group.

Contacts were defined as interactions between patients or caregivers and the health-care team (patient–professional interaction) which might be telematic with videoconference (preferable in the mHealth group) or face-to-face, planned or unplanned, which were required for the optimum monitoring of the disease, both in its normal course and in the event of the appearance of complications during the patient's follow-up. Unplanned contacts (face-to-face or remote) were defined as those made for any need (eg, clinical worsening, treatment adjustment, or other reasons) requested by the care team or by the participant themselves, without being previously planned, as opposed to a planned contact (programmed and scheduled at the beginning of the follow-up).

In addition to usual care, follow-up in the mHealth group was based on a digital intervention designed and modelled for individuals with heart failure: the Platform for the Provision of Teleintervention, Remote Monitoring and Empowerment to People with Advanced/Complex Chronic Disease based on eHealth (PIRENe; appendix 1 p 3).[21] Briefly, participants in the mHealth group were telemonitored and followed up according to a specific clinical pathway that included preplanned structured follow-up contacts with the health-care team. All participants in the mHealth group sent their daily biometric data (blood pressure, heart rate, and weight) via mHealth (smartphone app) connected to the medical devices (bodyweight scale and heart rate and blood pressure monitor). In addition, they completed a predefined daily symptom questionnaire via the mHealth app concerning heart failure status.[21] These data were received and collected via the PIRENe platform and analysed every day by the health-care team of each centre. In the event of data not being received, of any altered biomedical data or warning answers in the questionnaire, an alarm system was activated, allowing for proactive intervention by the health-care team based on workflow recommendations prespecified in the protocol and implemented per each centre's local practice. Finally, from the platform, all contacts (teleintervention) could be made via videoconference. We made assessments of mHealth acceptance, literacy, and adherence, as described in appendix 1 (pp 4–5). Daily monitoring of adherence to mHealth app involved potential triggering of a no data sent alarm if a patient did not send biomedical data or did not submit the daily questionnaire. This monitoring was supplemented by monthly assessments of transmission and use of data from the platform from the trial coordinating team.

In both study groups, signs or symptoms suggestive of decompensation could lead the health-care team to make adjustments to diuretic treatment according to the patient's needs and in accordance with previously defined and published algorithms,[21] and unplanned face-to-face or remote contacts could be performed at the health-care team's discretion. Regardless of the study group, all participants or caregivers could also make unplanned contact with the health-care team during working hours, depending on the availability of each heart failure unit, when necessary. Finally, in both groups, guideline-directed medical treatment adjustment[1] was promoted with no distinctions according to treatment group.

Outcomes

The primary outcome was a composite of the occurrence of cardiovascular death or a worsening heart failure event (first and recurrent) during the 6-month follow-up period. A worsening heart failure event was defined as a new episode of worsening symptoms and signs consistent with acute decompensated heart failure requiring intravenous decongestive therapy (eg, diuretics) either on an outpatient basis (eg, day-case heart failure hospital or at home) or in the emergency department (<24 h), requiring unplanned hospital admission (≥24 h), or complicating the course of a cardiovascular or non-cardiovascular hospital admission. A fatal event was defined as cardiovascular if it was the outcome of an acute coronary syndrome, worsening heart failure, stroke (ischaemic or haemorrhagic), pulmonary embolus, a complication of a cardiovascular intervention (surgical or percutaneous coronary revascularisation, implantation of pacemaker or implantable cardioverter-defibrillator or cardiac resynchronisation therapy, electrical cardioversion, electrophysiological study, vascular surgery, valvular surgery, heart transplant, or left ventricular assist device implant), cardiovascular haemorrhage (excluding traumatic cases), or any other less frequent cardiovascular causes.

The main clinical secondary outcomes were the components of the primary outcome analyses (worsening heart failure and cardiovascular death). Other clinical secondary outcomes were unplanned hospitalisations (for ≥24 h) due to all causes, heart failure, cardiovascular causes, and non-cardiovascular causes; urgent heart failure visits; and deaths due to all causes, heart failure, and non-cardiovascular causes. Urgent heart failure visits were acute worsening heart failure events requiring intravenous decongestive therapy (eg, diuretics) either on an outpatient basis (eg, day-case heart failure hospital or at home) or in the emergency department (<24 h). Heart failure hospitalisations and urgent heart failure visits were components of worsening heart failure events. The masked clinical endpoint committee adjudicated all clinical events occurring during the study according to prespecified criteria.[21]

Other secondary outcomes comprised the change from baseline in patient-reported outcome measures (PROMs; comprising QoL and self-care) and patient-reported experience measures (PREMs) relating to heart failure management satisfaction at the end of the 6-month follow-up. Patient-reported QoL was evaluated with the 3-level version of the EuroQol five-dimension questionnaire (EQ-5D-3L) with the visual analogue scale (EQ VAS)[24]; the patient evaluated their state of health, first in levels of severity by five dimensions (mobility, personal care, daily activities, pain/discomfort, and anxiety/depression; descriptive system) and then in a more general assessment consisting of a VAS ranging from 0 (worst imaginable health condition) to 100 (best imaginable health condition). The EQ-5D-3L index score ranges from 0 to 1, with higher scores indicating better patient-reported health status; the index score was calculated only if responses were available from all five questions. Patient-reported self-care was assessed with the European Heart Failure Self-Care Behaviour Scale (EHFScBS).[25] The EHFScBS consists of a self-administered 12-item questionnaire addressing different aspects of patient self-care. Each item is scored from 1 (completely agree or always) to 5 (completely disagree or never) and the overall score (calculated as the sum of scores for each item) varies from 12 (best self-care) to 60 (worst self-care). For the analysis of PREMs, we did a Net Promoter Score (NPS) analysis to assess the satisfaction of patients with the follow-up (appendix 1 p 4).[26,27]

We also assessed the number of contacts (planned, unplanned, and total number) made between participants or caregivers and the health-care team in both groups, the number of mHealth-system-generated alarms (overall and categorised by reason for the alarm) during monitoring in the mHealth group (post hoc), adherence with the non-invasive mHealth app on patient devices in the mHealth group (post hoc), and changes regarding the use and up-titration of heart failure disease-modifying drugs in both groups.

Other secondary outcomes, including days in hospital and emergency visits, cost utility, and QoL by the Minnesota Living with Heart Failure Questionnaire, were specified in the protocol but not included in the statistical analysis plan and are thus not reported.

Statistical analysis

Details regarding the power calculation have been published previously.[21] Briefly, our assumptions and resulting sample size calculations were based on previous data from the iCOR randomised trial, with an expected 6% screening dropout rate using a continuity-corrected calculation.[28] Accordingly, to obtain a clinically meaningful difference between the treatment groups of 13 percentage points in the proportion of patients with the composite primary outcome after 6 months of follow-up (49% participants with an event in the usual care group and 36% in the mHealth group) and assuming an alpha risk of 0·05 and a beta error of 20%, we calculated that we needed to recruit 508 participants from a target screening sample of 540 patients.

All the analyses were done on the full analysis set according to the intention-to-treat principle. We prespecified data analyses in the complete statistical analysis plan after the last patient's last visit and before the database lock (Dec 19, 2022). The statistical analysis plan is provided in appendix 3. Some outcome definitions were updated in the statistical analysis plan leading to minor differences between the trial protocol and statistical analysis plan; further details on these amendments are provided in appendix 1 (pp 40–41).

See Online for appendix 3

Baseline characteristics were summarised by study group. Baseline categorical variables were presented as number and percentages. Baseline continuous variables were presented as the mean (SD) or median (IQR) where required. Continuous variables were compared between the two groups using Student's *t* test or Mann–Whitney *U* test

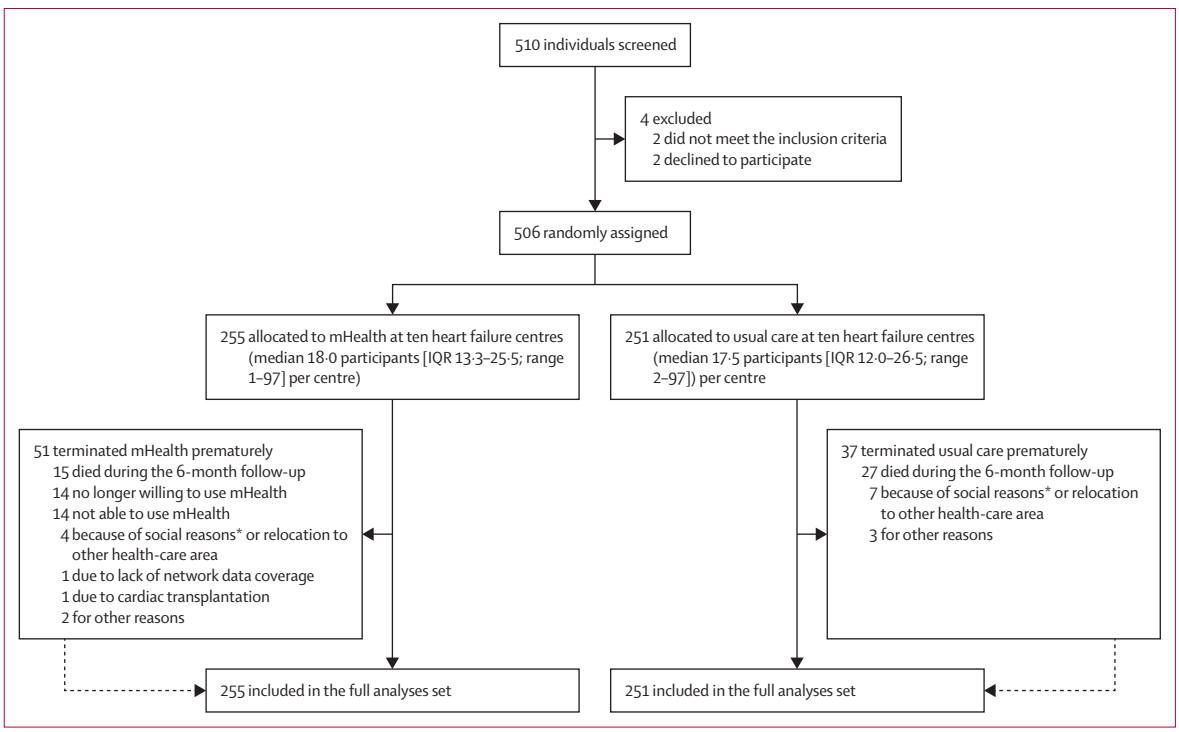


Figure 1: **Flowchart of study participants**
mHealth=mobile health technology. *Social reasons included poor social support or absence of support, or low socioeconomic status, which prevented optimal follow-up in the context of the trial.

where appropriate. Fisher's exact test or Pearson's χ^2 test were applied to assess the relationship between categorical variables.

The primary and secondary efficacy analyses of clinical events were done in accordance with time-to-first-event analyses. The incidence of first events in the two study groups were described using Kaplan–Meier survival functions. Cox proportional hazards models with randomisation group and centre as fixed-effect factors were used to obtain the hazard ratio (HR) for the first occurrence of each of the outcomes under study by comparing mHealth (as the exposure variable) with usual care as the reference group. Event rates were expressed as the number of total events per 100 patient-years of follow-up, accounting for censoring of follow-up data. Patients were censored if lost to follow-up due to death, transplantation, or ventricular assist implantation (where the transplantation or implantation events led to early termination of study follow-up). Losses to follow-up for other reasons, such as poor adherence or social problems, were not censored given that all data on clinical events were available 6 months after inclusion in the study for all patients regardless of whether the patients were lost to follow-up (intention-to-treat analysis). Relative risk reduction (RRR), expressed as percentage, was calculated from HR using the formula RRR = (1 – HR) × 100, with 1 as the reference value for the control group (usual care). The same formula was applied to calculate 95% CIs for RRR using the 95% CIs for the HR. The number needed to treat, defined as the number of people who need to be treated to prevent one additional outcome (first) event, was calculated from the absolute risk reduction (ARR) between the mHealth group and the usual care group for the primary outcome (first event). The event rate in the control group was calculated using the number of events in the usual care group divided by the total number of patients in the group. The event rate in the mHealth group corresponded to the HR of this group. The ARR was the difference between the two event rates. Number needed to treat was calculated as 1/ARR.

We assessed the consistency of the mHealth-based follow-up on the primary outcome (time to first event) in prespecified subgroups (appendix 1 pp 6–7) and according to study centre and heart failure care setting post hoc. A statistical test of interaction was done to assess the robustness of the effect of mHealth on the primary outcome in the different subgroups.

Recurrent-event analyses for the primary outcome were also done, estimating mean cumulative function from a fitted gamma frailty model obtained from the recurrent event data using a non-parametric mean cumulative function estimator (the Nelson–Aelen estimator of the cumulative hazard function). Rate ratios were calculated accordingly.

In addition, post-hoc Cox regression estimation of intraclass correlations was done as a sensitivity analysis for the primary outcome and secondary clinical outcomes (time to first event) to assess the potential effects of clustering by

	mHealth (n=255)	Usual care (n=251)
Age, years	73 (13)	73 (12)
Gender		
Women	111 (44%)	96 (38%)
Men	144 (56%)	155 (62%)
New York Heart Association functional class		
I	30 (12%)	29 (12%)
II	160 (63%)	164 (65%)
III	64 (25%)	55 (22%)
IV	1 (<1%)	3 (1%)
Primary cause of heart failure		
Coronary artery disease	80 (31%)	73 (29%)
Hypertension	53 (21%)	41 (16%)
Valve disease	48 (19%)	50 (20%)
Alcoholic	6 (2%)	11 (4%)
Idiopathic	17 (7%)	25 (10%)
Other	51 (20%)	51 (20%)
Classification of heart failure*		
Heart failure with reduced ejection fraction	111 (44%)	117 (47%)
Heart failure with mildly reduced ejection fraction	37 (15%)	29 (12%)
Heart failure with preserved ejection fraction	107 (42%)	105 (42%)
LVEF, %	45% (16)	45% (17)
Biometric data		
Blood pressure, mm Hg		
Systolic	122 (21)	119 (19)
Diastolic	69 (12)	69 (12)
Heart rate, bpm	75 (16)	75 (16)
BMI, kg/m^2	29 (7)	28 (6)
More than one hospital admission in the past 12 months		
All-cause	92 (36%)	100 (40%)
Cardiovascular cause	63 (25%)	72 (29%)
Cardiovascular risk factors		
Smoking status		
Smoker	36 (14%)	37 (15%)
Former smoker	94 (37%)	98 (39%)
Non-smoker	125 (49%)	116 (46%)
Hypertension	187 (73%)	190 (76%)
Hyperlipidaemia	156 (61%)	153 (61%)
Type 1 or type 2 diabetes	99 (39%)	109 (43%)
Obesity†	84 (33%)	95 (38%)
Comorbidities		
Atrial fibrillation	111 (44%)	99 (39%)
Chronic kidney disease‡	154 (60%)	151 (60%)
Iron deficiency§	167 (65%)	152 (61%)
Anaemia¶	111 (44%)	123 (49%)
Chronic lung disease	69 (27%)	65 (26%)
Peripheral artery disease	34 (13%)	37 (15%)
Moderate to severe chronic liver disease‖	3 (1%)	2 (1%)
Cerebrovascular disease	23 (9%)	35 (14%)
Depression or other major psychiatric disorders**	18 (7%)	17 (7%)
Charlson Comorbidity Index	3·3 (1·8)	3·2 (1·9)

(Table 1 continues in next column)

	mHealth (n=255)	Usual care (n=251)
(Continued from previous column)		
Treatment		
Angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker	118 (46%)	114 (45%)
Angiotensin receptor neprilysin inhibitor	56 (22%)	60 (24%)
β blocker	217 (85%)	206 (82%)
Mineralocorticoid receptor antagonist	107 (42%)	96 (38%)
Loop diuretics	248 (97%)	235 (94%)
Thiazide diuretics	29 (11%)	32 (13%)
Ivabradine	14 (5%)	10 (4%)
Hydralazine	22 (9%)	21 (8%)
Nitrate	29 (11%)	36 (14%)
Amiodarone	34 (13%)	30 (12%)
Digoxin	16 (6%)	19 (8%)
Antiplatelet therapy	75 (29%)	80 (32%)
Anticoagulant therapy		
Direct oral anticoagulants	88 (35%)	89 (35%)
Vitamin K antagonists	62 (24%)	52 (21%)
Cardiac devices		
Implantable cardioverter-defibrillator	16 (6%)	9 (4%)
Cardiac resynchronisation therapy	5 (2%)	6 (2%)
Laboratory measurements		
Haemoglobin, g/dL	13 (2)	13 (2)
eGFR, mL/min per 1·73 m^2	56 (23)	55 (22)
Sodium, mmol/L	140 (4)	140 (4)
Potassium, mmol/L	4 (0·6)	4 (0·6)
N-terminal pro-B-type natriuretic peptide, pg/mL	4681 (1138–4884)	4305 (1495–5195)
Frailty (per FRAIL scale††)		
Non-frail	91 (36%)	64 (25%)
Prefrail	99 (39%)	115 (46%)
Frail	65 (25%)	72 (29%)
Social resources		
Home-based care	13 (5%)	12 (5%)
Living alone	48 (19%)	50 (20%)
Need for caregiver	137 (54%)	143 (57%)
Need for social resource‡‡	50 (20%)	51 (20%)
Support needed to take medication	147 (58%)	151 (60%)
Monthly income, € (n=266)	1000 (1141–4876)	1000 (1499–5178)
Functional status (Barthel index)	93 (12)	91 (16)
Literacy		
Less than primary education (<6 years of formal education)	15 (6%)	13 (5%)
Primary education (6–12 years of formal education)	173 (68%)	149 (59%)
Secondary or higher education (>12 years of formal education)	67 (26%)	89 (35%)
Cognitive impairment§§	24 (9%)	30 (12%)

(Table 1 continues on next page)

	mHealth (n=255)	Usual care (n=251)
(Continued from previous page)		
ICT skills and resources		
Lower ICT skills¶¶	140 (55%)	143 (57%)
No internet at home	99 (39%)	90 (36%)
Does not own a computer or tablet	130 (51%)	129 (51%)
Does not own a smartphone	111 (44%)	113 (45%)

Data are presented as arithmetic mean (SD), n (%), or median (IQR). eGFR=estimated glomerular filtration rate. ICT=information and communications technology. LVEF=left ventricular ejection fraction. mHealth=mobile health technology. *Classification according to European Society of Cardiology criteria[1] based on LVEF (heart failure with reduced ejection fraction: LVEF ≤40%; heart failure with mildly reduced ejection fraction: LVEF 41–49%; and heart failure with preserved ejection fraction: LVEF ≥50%). †Obesity was defined by the WHO criteria (BMI ≥30 kg/m^2). ‡Chronic kidney disease was defined as eGFR <60 mL/min per 1·73 m^2. §Iron deficiency was defined as ferritin <100 ng/mL or transferrin saturation <20%. ¶Anaemia was defined by the WHO criteria (haemoglobin <12 g/dL in women and <13 g/dL in men). ||Moderate to severe chronic liver disease was defined as chronic liver disease with evidence of portal hypertension (ascites, oesophageal varices or encephalopathy). **Depression or other major psychiatric disorders were defined as psychiatric disorders or depression of prolonged duration that entailed a variable degree of disability and social dysfunction, and requiring care in various care resources of the health and social care network. ††The FRAIL scale,[32] which was different from the frailty stratification criteria used for randomisation, was based on a phenotypic model including five items contributing to patient frailty: fatigue, resistance, ambulation, illnesses, and loss of weight. Scores of 3–5 indicate frail health status, 1–2 indicate prefrail health status, and 0 indicates normal health status. ‡‡Need for social resource was defined according to the requirement or utilisation of at least one of the following social resources: tele-assistance, home-delivered food, home cleaning, day care centre attendance, or attendance at food centres. §§Cognitive impairment was defined by at least three errors on the Pfeiffer Short Portable Mental Status Questionnaire or a diagnosis of dementia in the corresponding section of the Charlson Comorbidity Index. ¶¶ICT skills were evaluated with a patient-reported Likert scale from 0 to 5 where 0 was no difficulties and 5 was a lot difficulties in ICT handling; scores of 3–5 were designated as lower ICT skills.

Table 1: **Baseline characteristics of study participants (full analysis set)**

participating centre using recommended intraclass correlation coefficient cutoff values.[29,30]

Changes from baseline to the end of follow-up in continuous variables for PROMs were compared by repeated-measures ANCOVA models with randomisation group, centre, and baseline PROMs scores as fixed-effect factors. A responder analysis of the EQ-5D-3L index score was also done, in which a minimal clinically important difference was considered as an improvement equal to or greater than 0·074 on the EQ-5D-3L index score.[31] PREMs were assessed using NPS described in percentages. ANOVA models were implemented to compare the three NPS-defined groups (detractors, passives, and promoters) within each group (overall study population, usual care, and mHealth). Imputation methods used to account for missing data relating to PROMs and PREMs are described in appendix 1 (p 8).

The use of disease-modifying heart failure drugs at baseline and at the end of the study was compared between the study groups, and, as a categorical variable, was presented as the number of cases and percentage. A Pearson's χ^2 test was applied to assess drug use across categories of heart failure according to LVEF.[1]

Continuous variables related to the number of planned or unplanned post-discharge health-care contacts (including, the number of worsening heart failure episodes managed in the ambulatory setting with increased oral diuretic [post-hoc outcome] or with intravenous or subcutaneous furosemide [a component of the primary outcome]) were presented as frequency and median (IQR) and were compared between the two groups using Student's *t* test. In these analyses, outcomes regarding the management of worsening heart failure pertained to the ambulatory setting only (ie, the outpatient setting or an emergency department visit for <24 h), with worsening heart failure defined as new episodes of worsening symptoms and signs consistent with acute decompensated heart failure, without requiring hospital admission. Increased oral diuretic was defined as an increased dose of any diuretic or initiation of thiazides among other diuretics in combination.

For post-hoc analyses of data collected from the mHealth-based app, the absolute number of alarms recorded by the mHealth system was reported overall (within the mHealth group) and per patient (median and IQR). Adherence to the eHealth system was estimated based on the number of interactions with the app (sending biomedical data or responding to the daily questionnaire) on days when the optimal follow-up was possible, when the patient was able to submit the questionnaire and biomedical measurements on a daily basis, excluding any days when a patient was admitted to hospital during follow-up. Regarding transmission of biomedical data, adherence was calculated by dividing all days with data transmission by the total number of days for each patient, multiplied by 100. The final percentage represented the arithmetic mean for all patients for each biomedical measurement transmitted. A similar calculation was done to determine questionnaire adherence based on complete questionnaires that were submitted.

All statistical tests and 95% CIs were constructed with a type I error alpha level of 5%, with no adjustments for multiplicity. Two-sided p values of less than 0·05 were considered to indicate statistical significance. Analyses were done with SPSS software (version 25.0) and R software (version 4.0.2).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From May 15, 2018, to April 4, 2022, 510 individuals were screened, of whom 506 were randomly assigned (255 to mHealth and 251 to usual care). This sample had two fewer than the 508 participants indicated by the power calculation. Four patients were excluded due to not meeting the inclusion criteria (n=2) or declining to participate (n=2). Follow-up ended prematurely in 51 (20%) of

	mHealth (n=255)			Usual care (n=251)				
	Total events (first and recurrent)	Patients with event (%)	Events (first and recurrent) per 100 patient-years	Total events (first and recurrent)	Patients with event (%)	Events (first and recurrent) per 100 patient-years	Time-to-first-event hazard ratio (95% CI)*	p value
Primary outcome and its components								
Cardiovascular death or worsening heart failure	64	43 (17%)	55·4	168	102 (41%)	196·5	0·35 (0·24–0·50)	<0·0001
Cardiovascular death†	10	10 (4%)	8·0	20	20 (8%)	16·6	0·46 (0·22–0·99)	0·047
Worsening heart failure†	54	36 (14%)	47·3	148	99 (39%)	167·2	0·30 (0·20–0·44)	<0·0001
Clinical secondary outcomes								
Heart failure hospitalisation‡	23	18 (7%)	18·9	63	50 (20%)	28·7	0·29 (0·17–0·49)	<0·0001
Cardiovascular hospitalisation	38	29 (11%)	32·2	71	58 (23%)	65·9	0·44 (0·28–0·70)	<0·0001
Non-cardiovascular hospitalisation	38	33 (13%)	32·2	48	35 (14%)	42·2	0·91 (0·57–1·47)	0·71
All-cause hospitalisation	76	57 (22%)	70·0	119	86 (34%)	124·3	0·59 (0·43–0·83)	0·0020
Urgent heart failure visit‡	21	17 (7%)	17·1	62	46 (18%)	56·4	0·33 (0·19–0·57)	<0·0001
Heart failure death	6	6 (2%)	4·8	18	18 (7%)	14·8	0·31 (0·12–0·77)	0·012
Non-cardiovascular death	5	5 (2%)	4·0	7	7 (3%)	5·7	0·65 (0·21–2·04)	0·46
All-cause death	15	15 (6%)	12·1	27	27 (11%)	22·7	0·51 (0·27–0·96)	0·036

mHealth=mobile health technology. *mHealth versus usual care (reference category) with randomisation group and centre as fixed-effect factors. †Also a secondary outcome. ‡Components of worsening heart failure events; worsening heart failure events also included cardiovascular or non-cardiovascular hospitalisations complicated by heart failure.

Table 2: **Prespecified primary and secondary clinical outcomes according to treatment group (full analysis set)**

255 participants in the mHealth group and 37 (15%) of 251 in the usual care group (figure 1). The distribution of enrolled participants by centre and care setting is described in appendix 1 (p 9).

Baseline variables were similar between the mHealth and usual care groups (table 1). Overall, mean age was 73 years (SD 13); 207 (41%) of 506 participants were women and 299 (59%) were men. Advanced heart failure symptoms (New York Heart Association functional class III–IV) were recorded in 65 (25%) of 255 participants in the mHealth group and 58 (23%) of 251 in the usual care group. Heart failure with preserved ejection fraction was recorded in 212 (42%) of 506 participants, and 153 (30%) had an ischaemic cause of heart failure. A high burden of comorbidity was observed (overall mean Charlson Comorbidity Index of 3·3 [SD 1·8]). Regarding psychosocial characteristics, 137 (27%) of 506 participants met frailty criteria per the FRAIL scale[32] and 280 (55%) had the need for a caregiver. Baseline literacy levels and individual abilities relating to information and communication technology (ICT) were predominantly low. Most patients were receiving multidisciplinary or cardiology specialist care (appendix 1 p 9).

In the overall study population, the composite primary outcome of cardiovascular death or a worsening heart failure event occurred in 145 participants during the 6-month follow-up: in 43 (17%) of 255 in the mHealth group and 102 (41%) of 251 in the usual care group (table 2). In the mHealth group, there were 54 total events (first and recurrent) of worsening heart failure, compared with 148 in the usual care group. Events of worsening heart failure were heart failure hospitalisation (23 in the mHealth group and 63 in the usual care group), urgent heart failure visit (21 in the mHealth group and 62 in the usual care group), and other-cause (cardiovascular or non-cardiovascular) hospitalisation complicated due to heart failure (ten in the mHealth group and 23 in the usual care group). Regarding cardiovascular death, ten (4%) of 255 participants in the mHealth group died of cardiovascular causes during follow-up, in comparison to 20 (8%) of 251 in the usual care group (table 2).

The risk of having a primary outcome event (first event) was statistically significantly lower in participants allocated to the mHealth group versus those allocated to usual care (HR 0·35 [95% CI 0·24–0·50]; p<0·0001; figure 2A) with an RRR of 65% (95% CI 50–76), equating to a number needed to treat of 3·8. Post-hoc sensitivity analysis accounting for possible clustering by study centre is presented in appendix 1 (pp 10–11), which yielded results that were consistent with the main analysis.

The incidence of both primary outcome components favoured the mHealth group. Risk of a first event of worsening heart failure (HR 0·30 [95% CI 0·20–0·44]; p<0·0001; RRR 70% [95% CI 56–80]) and of cardiovascular death (HR 0·46 [0·22–0·99]; p=0·047; RRR 54% [1–78]) was reduced among participants given access to mHealth (figure 2B, C). The benefit of mHealth compared with usual care for the primary outcome was sustained in recurrent-event analyses (rate ratio 0·34 [95% CI 0·23–0·51]; p<0·0001; appendix 1 p 12).

Regarding secondary outcomes, the risk of a first occurrence of all prespecified non-fatal events was statistically significantly higher in the usual care group than in the mHealth group except for non-cardiovascular hospitalisation (table 2, appendix 1 pp 13–16). Reductions in all-cause hospitalisations and all-cause deaths observed in the mHealth group compared with the usual care group appeared to be attributable to a reduction in the number of cardiovascular hospitalisations and deaths, and particularly

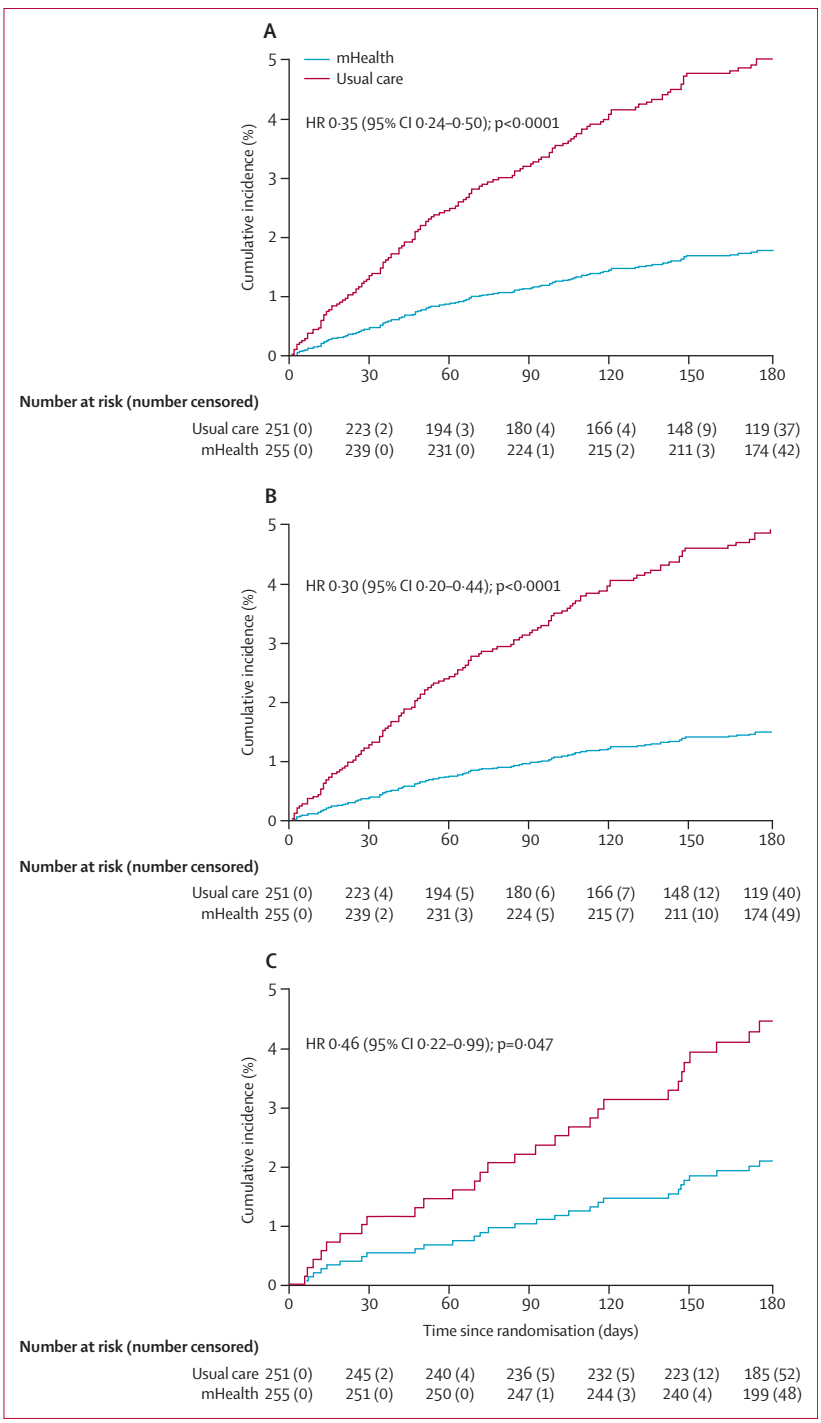


Figure 2: **Cumulative survival curves for the composite primary outcome and its components (worsening heart failure and cardiovascular death) according to treatment group (full analysis set)**
Plots show Kaplan–Meier curves for the cumulative incidence of a first event over time and HRs from Cox regression time-to-first-event models for the composite primary outcome (A), for worsening heart failure (B), and for cardiovascular death (C). HR=hazard ratio. mHealth=mobile health technology.

those related to heart failure (table 2, figure 2C, appendix 1 pp 13–16). Reduced all-cause mortality appeared to be attributable to reduced risk of death due to heart failure (RRR 69% [95% CI 23–88]) combined with a reduced overall risk of cardiovascular death. No statistically significant difference was identified between the two groups in terms of non-cardiovascular death. Post-hoc intraclass correlation analysis for secondary outcomes excluded the possibility of bias due to clustering within centres (intraclass correlation coefficient values <0·5; appendix 1 pp 10–11).

The effect of mHealth on first occurrence of the primary composite outcome was consistent with no significant heterogeneity across most prespecified subgroups, including those defined by age, frailty status, and heart failure classification based on LVEF, as well as other relevant clinical and psychosocial variables. However, there was significant heterogeneity in response to mHealth by gender, and, in post-hoc analysis, according to heart failure care setting (figure 3, appendix 1 p 17).

Baseline PROMs for QoL and self-care were similar between the groups. Participants in the mHealth group had a statistically significantly greater improvement in both PROMs than patients in the usual care group at 6 months (table 3). Both self-care and EQ VAS showed a statistically significant greater change over time with mHealth versus usual care, but this was not seen in the EQ-5D-3L index score. When investigated using the responder analysis of index score data, the proportion of patients with a minimal clinically important difference (improvement ≥0·074 on the EQ-5D-3L index score[31]) appeared to be higher in the mHealth group than in the usual care group. The difference was statistically significant with non-imputed data (72 [34%] of 212 participants in the mHealth group *vs* 56 [27%] of 207 in the usual care group; p=0·025) and numerically different, albeit not statistically significant, with imputed data (92 [36%] of 255 *vs* 76 [30%] of 251 in the usual care group; p=0·12).

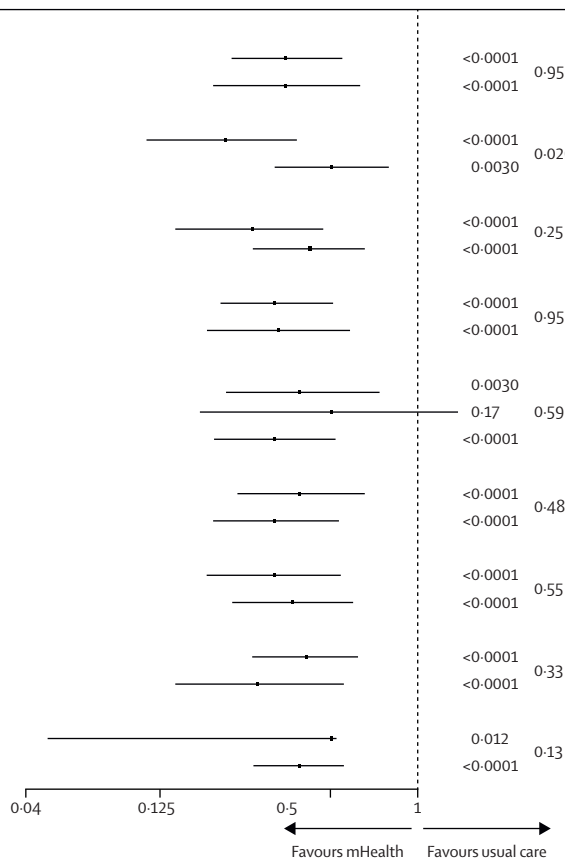
At the end of the follow-up, we observed excellent overall satisfaction according to global NPS in both groups (mHealth group: global NPS promoters 79%, passives 14%, and detractors 7%; and usual care group: promoters 77%, passives 17%, and detractors 6%) and a statistically significant difference in favour of mHealth over usual care based on the imputed dataset (p<0·0001; n=82 [16%] imputations; appendix 1 p 18).

At the end of follow-up, statistically significantly more visits (total and unplanned [mainly unplanned]) were recorded in the mHealth group than in the usual care group (appendix 1 p 19). Similarly, the proportion of episodes of worsening heart failure treated with oral diuretic up-titration was statistically significantly higher in the mHealth group than in the usual care group when assessed post hoc (table 3). Conversely, the proportion of episodes of worsening heart failure treated with ambulatory intravenous or subcutaneous furosemide was statistically significantly higher in the usual care group than in the mHealth group.

We did not observe any clinically meaningful differences in the use of disease-modifying drugs for heart failure

A

Subgroups	Patients (%)	mHealth: patients with event (%)	Usual care: patients with event (%)	HR (95% CI)*	p value	p value for interaction†
Age, years						
≥75	263 (52%)	27 (21%)	63 (48%)	0·34 (0·22–0·54)	<0·0001	0·95
<75	243 (48%)	16 (13%)	39 (33%)	0·34 (0·19–0·62)	<0·0001	
Gender						
Women	207 (41%)	15 (14%)	47 (49%)	0·21 (0·11–0·37)	<0·0001	0·026
Men	299 (59%)	28 (19%)	55 (36%)	0·49 (0·31–0·78)	0·0030	
Frailty‡						
Frail	161 (32%)	16 (19%)	41 (53%)	0·26 (0·14–0·46)	<0·0001	0·25
Non-frail	345 (68%)	27 (16%)	61 (35%)	0·41 (0·26–0·64)	<0·0001	
New York Heart Association functional class						
I or II	383 (76%)	24 (13%)	67 (35%)	0·31 (0·20–0·50)	<0·0001	0·95
III or IV	123 (24%)	19 (29%)	35 (60%)	0·32 (0·18–0·57)	<0·0001	
Classification of heart failure						
Heart failure with reduced ejection fraction	228 (45%)	14 (13%)	37 (32%)	0·38 (0·21–0·72)	0·0030	
Heart failure with mildly reduced ejection fraction	66 (13%)	7 (19%)	10 (35%)	0·49 (0·17–1·36)	0·17	0·59
Heart failure with preserved ejection fraction	212 (42%)	22 (21%)	55 (52%)	0·31 (0·19–0·51)	<0·0001	
Type 1 or 2 diabetes						
Yes	208 (41%)	21 (21%)	49 (45%)	0·38 (0·23–0·64)	<0·0001	0·48
No	298 (59%)	22 (14%)	53 (37%)	0·31 (0·19–0·52)	<0·0001	
Atrial fibrillation						
Yes	210 (42%)	19 (17%)	44 (44%)	0·31 (0·18–0·53)	<0·0001	0·55
No	296 (58%)	24 (17%)	58 (38%)	0·36 (0·22–0·58)	<0·0001	
Chronic kidney disease						
Yes	305 (60%)	32 (21%)	65 (43%)	0·40 (0·26–0·61)	<0·0001	0·33
No	201 (40%)	11 (11%)	37 (37%)	0·27 (0·14–0·54)	<0·0001	
Depression or other major psychiatric condition						
Yes	35 (7%)	1 (6%)	8 (47%)	0·49 (0·05–0·51)	0·012	0·13
No	471 (93%)	42 (18%)	94 (40%)	0·38 (0·26–0·54)	<0·0001	



(Figure 3 continues on next page)

between baseline and the end of follow-up (appendix 1 pp 20–21). No cases of spontaneously reported harms were recorded in response to changes in treatment.

Although expected, statistically significant differences in treatment according to LVEF across the study groups were observed, with the use of disease-modifying heart failure drugs generally being the highest in patients with heart failure with reduced ejection fraction. There were no statistically significant differences according to treatment group, apart from for loop diuretics at baseline among participants with preserved ejection fraction (significantly more patients receiving loop diuretics in the mHealth group *vs* usual care group), indicating equality of care between the groups other than access to mHealth (appendix 1 pp 20–21).

In post-hoc assessment of mHealth alarms, a total of 11 012 alarms (any warning) were generated from the PIRENe platform during the 6-month follow-up in the mHealth group (appendix 1 p 22). 3224 (29%) of 11 012 alarms were due to an affirmative response in the daily signs and symptoms questionnaire leading to reporting an adverse condition in the questionnaire.

A total number of 45 900 questionnaires were administered for daily monitoring of heart failure signs and symptoms, of which 21 708 (47%) were completed. Concerning biometric data submission, 71 028 measurements were sent: 33 912 (48%) weight measurements and 37 116 (52%) blood pressure and heart rate measurements. Adherence to the mHealth-based solution, assessed by timely provision of biometric data or response to the daily signs and symptoms questionnaire, was analysed post hoc. mHealth adherence regarding transmission of biomedical data was observed to be a mean of 77% in the mHealth group. The degree of compliance was slightly lower, at 67% with regard to responses to the daily signs and symptoms questionnaire.

Discussion

The HERMeS trial results showed that mHealth-based heart failure care combining teleintervention and telemonitoring

B

Subgroups	Patients (%)	mHealth: patients with event (%)	Usual care: patients with event (%)	HR (95% CI)*	p value	p value for interaction†
Comorbidity						
High	187 (37%)	19 (20%)	44 (48%)	0·30 (0·17–0·52)	<0·0001	0·78
Low	319 (63%)	24 (15%)	58 (37%)	0·36 (0·22–0·57)	<0·0001	
N-terminal pro-B-type natriuretic peptide pg/mL						
≥ median	253 (50%)	29 (23%)	51 (41%)	0·46 (0·29–0·73)	0·0010	0·065
< median	253 (50%)	14 (11%)	51 (40%)	0·21 (0·11–0·38)	<0·0001	
Dependency for activities of daily living						
Yes	213 (42%)	20 (19%)	57 (53%)	0·26 (0·16–0·44)	<0·0001	0·20
No	293 (58%)	23 (15%)	45 (32%)	0·46 (0·28–0·75)	0·0020	
Cognitive impairment						
Yes	54 (11%)	3 (13%)	18 (60%)	0·13 (0·03–0·52)	0·0040	0·17
No	452 (89%)	40 (17%)	84 (38%)	0·39 (0·24–0·54)	<0·0001	
Living alone						
Yes	98 (19%)	9 (19%)	24 (48%)	0·30 (0·13–0·68)	0·0040	0·74
No	408 (81%)	34 (16%)	78 (39%)	0·36 (0·22–0·57)	<0·0001	
Need for caregiver						
Yes	280 (55%)	25 (18%)	64 (45%)	0·33 (0·21–0·52)	<0·0001	0·68
No	226 (45%)	18 (15%)	38 (35%)	0·39 (0·22–0·69)	0·0010	
Self-care						
Impaired	263 (52%)	21 (16%)	45 (35%)	0·40 (0·24–0·67)	0·0010	0·48
Preserved	243 (48%)	22 (18%)	57 (47%)	0·30 (0·18–0·50)	<0·0001	
Literacy						
Lower	350 (69%)	32 (17%)	75 (46%)	0·29 (0·19–0·44)	<0·0001	0·74
Middle or higher	156 (31%)	11 (16%)	27 (30%)	0·30 (0·18–0·50)	0·069	
ICT skills						
Lower	283 (56%)	25 (18%)	68 (48%)	0·29 (0·18–0·46)	<0·0001	0·29
Middle or higher	223 (44%)	18 (16%)	34 (32%)	0·43 (0·24–0·76)	0·0040	
Overall population	506 (100%)	43 (17%)	102 (41%)	0·35 (0·24–0·50)	<0·0001	

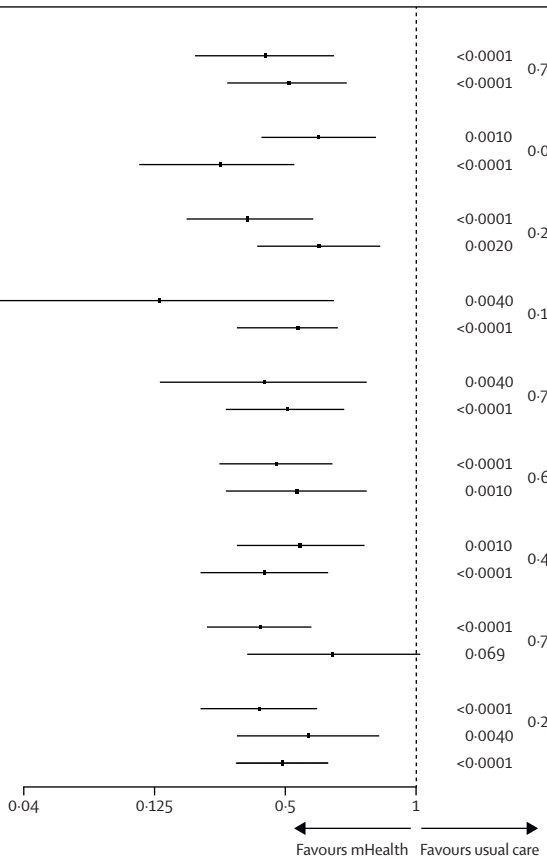


Figure 3: **Forest plot of primary outcome occurrence (first event) in prespecified subgroups (full analysis set)**
Definitions of subgroup variables are provided in appendix 1 (pp 6–7). The x-axis is presented on a logarithmic scale. HR=hazard ratio. ICT=information and communications technology. *mHealth versus usual care (reference category) with randomisation group and centre as fixed-effect factors. †Interaction between treatment group and prespecified subgroups in the incidence of the primary outcome. ‡Presence or absence of predefined frailty criteria described previously.[21]

prevented new fatal and non-fatal cardiovascular events compared with usual care in patients with a recent hospital admission due to heart failure decompensation. The positive effect of mHealth in this critical period was observed across most predefined subgroups, indicating that combining teleintervention and telemonitoring is useful in nearly all heart failure care settings and across most patient strata regardless of their baseline status. Integrating mHealth into heart failure management in the post-discharge vulnerable phase facilitated both planned and unplanned contacts between patients and health-care providers to allow rapid, effective mitigation of emergent heart failure decompensation events, including adjustment of guideline-directed medical treatment. There were no apparent safety issues relating to treatment changes, based on an absence of drug-related withdrawals from the trial and an absence of spontaneously reported adverse events.

To our knowledge, HERMeS represents the first trial to provide evidence for a beneficial effect of mHealth telemonitoring and teleintervention strategies in addition to guideline-concordant care in people with heart failure during the post-discharge vulnerable phase. Specifically, mHealth enabled early detection of adverse heart failure events and indicators of decompensation, as observed by the higher number of unplanned contacts, as opposed to planned contacts, in the mHealth group versus in the usual care group, enabling rapid intervention (eg, increased dosage of oral diuretics to abort the decompensation event). Avoiding or terminating decompensation events early via mHealth might help to reduce the health, humanistic, and economic burden of heart failure.[10] Although the requirements for implementing mHealth remain to be fully explored, the ability to help people with heart failure to remain out of hospital and manage symptoms using well established

	Baseline		End of study			
	mHealth (n=255)	Usual care (n=251)	mHealth (n=255)	Usual care (n=251)	Mean difference in change from baseline† (95% CI)	p value
PROMS						
EQ VAS score‡	61 (19)	63 (20)	74 (18)	70 (20)	10·41 (8·36 to 12·45)	<0·0001
EQ-5D-3L index score‡	0·7 (0·2)	0·7 (0·2)	0·8 (0·2)	0·7 (0·2)	0·02 (0·00 to 0·39)	0·12
Self-care score§	31 (11)	30 (10)	18 (6)	20 (6)	−11·43 (−12·33 to −10·52)	<0·0001
Worsening heart failure management*						
Total number of worsening heart failure episodes managed with increase of oral diuretic¶	NA	NA	270/425 (64%)	155/425 (36%)	..	<0·0001
Median (IQR) number of worsening heart failure episodes managed with increase of oral diuretic¶	..	..	0 (0 to 2)	0 (0 to 1)	..	<0·0001
Total number of worsening heart failure episodes managed with ambulatory intravenous or subcutaneous furosemide	NA	NA	21/83 (25%)	62/83 (75%)	..	<0·0001
Median (IQR) number of worsening heart failure episodes managed with ambulatory intravenous or subcutaneous furosemide	..	..	0 (0 to 0)	0 (0 to 0)	..	<0·0001

Data for PROMS are mean (SD); data for heart failure episodes are median (IQR) or n/N (%), where N represents the total number of worsening heart failure episodes managed with the specified treatment in the overall population. Results for PROMS represent the dataset with imputation for missing values (n=40 imputations per group per variable). EQ VAS=EuroQol visual analogue scale. EQ-5D-3L=EuroQol five-dimension three-level questionnaire. mHealth=mobile health technology. NA=not applicable. PROMs=patient-reported outcome measures. *In these analyses, worsening heart failure episode was defined as worsening symptoms and signs consistent with acute decompensated heart failure in the ambulatory setting, without requiring hospital admission. †Mean difference in the change from baseline in the mHealth group versus the change in the usual care group (reference category) with randomisation group, centre, and baseline PROMs scores as fixed-effect factors in repeated measures ANCOVA, accounting for all measurements of the variable rather than only the mean as a discrete variable. ‡Quality of life was evaluated with the EQ-5D-3L and EQ VAS; the patient evaluated their state of health, first in levels of severity by five dimensions (mobility, personal care, daily activities, pain/discomfort, and anxiety/depression; descriptive system) and then in a more general assessment consisting of a VAS ranging from 0 (worst imaginable health condition) to 100 (best imaginable health condition); the EQ-5D-3L index score ranges from 0 to 1, with higher scores indicating better patient-reported health status; the index score was calculated only if responses were available for all five dimensions. §Self-care was evaluated with the European Heart Failure Self-Care Behaviour Scale (score range 12–60, with higher scores indicating worse self-care).[24] ¶A post-hoc outcome; increase of oral diuretic was defined as increased dose of any diuretic or initiation of thiazides among other diuretics in combination.

***Table* 3: PROMs and use of diuretics to manage worsening heart failure episodes* according to treatment group (full analysis set)**

medications offers a fairly simple and straightforward approach to improving heart failure care in ambulatory individuals during the vulnerable phase. The potential to achieve guideline-directed medical treatment in these individuals without clinic visits, travel, or other logistics might offer benefits to all parties.

Although we did not include the requirement of oral diuretic dose escalation in the definition of worsening heart failure in the HERMeS protocol,[21] our findings that up-titration of oral diuretics was more frequent for worsening heart failure events in the mHealth group versus the usual care group, as anticipated, are in accordance with recent guidance on the early management of worsening heart failure during the vulnerable phase.[33] Conversely, patients in the usual care group appeared more likely than those in the mHealth group to require intravenous or subcutaneous diuretics. In the usual care group, decompensations were probably detected later than in the mHealth group, when the events were more evident, and when the participant was consulted (ie, when signs or symptoms were evident to the participant or health-care team) or when there was a scheduled visit. In these cases, there was no proactivity facilitated by the mHealth platform, potentially explaining why many patients receiving usual care were treated with intravenous or subcutaneous diuretics.

In HERMeS, we successfully combined daily telemonitoring and structured teleintervention by videoconferencing. BEAT-HF was another trial published in 2016 that combined telemonitoring and teleintervention, although it focused only on health coaching (health literacy) with telephone calls (soft intervention).[18] BEAT-HF showed no significant difference in any-cause readmissions between the intervention and usual care in a post-hospitalisation period of 180 days. The results of HERMeS underline the importance of combining appropriate telemonitoring and structured teleintervention that allows both scheduled and unplanned visits to optimally prevent further decompensation events. HERMeS is not comparable in design to other major trials such as TIM-HF,[16] or TELE-HF[13] in which patients tended to be less clinically vulnerable and more stable.

Integration of an eHealth-based solution into usual health-care systems and provision of a user-friendly interface for patients to promote adherence and persistence are two key aspects that likely contributed to the efficacy of mHealth in this trial. Digital intervention not connected to local health-care networks, such as in the TELE-HF trial[13] or in the SPAN-CHFII trial,[14] could be a key factor explaining the heterogeneity of clinical results in previously reported trials,[10] potentially underlying the lack of robustness in recommendations on digital solutions in heart failure management in clinical practice guidelines.[1] Embedding mHealth in the local clinical health-care context seemed to enable scalable, seamless transitions of care, and to increase confidence of participants in using the intervention, based on measurement of participant satisfaction (global NPS). The potential for scalable, flexible implementation at local, individual heart failure centres in a real-world setting was shown by favourable intraclass correlation values in correlation analyses adjusted for heart failure centres. However,

the analysis stratified by health-care setting showed that the effect of mHealth on the primary outcome had some heterogeneity according to the care setting in which the monitoring was conducted (appendix 1 p 17). These findings could provide the basis for future post-hoc analysis according to care models, as well as gender, among other variables, to explain and help to address these differences. We recognise that the additional number of alarms requiring an urgent response with mHealth might result in an incremental workload, with implication for staffing levels and workflows, which would need to be addressed in routine implementation of mHealth. Additional investigations are needed to assess the impact of this mHealth programme on staff roles and responsibilities, as well as any training or recruitment needs (eg, adequate response times to alarms) to work with this new model of care.

Our results show that mHealth not only had a clinical effect in reducing events of worsening heart failure, hospitalisations, and deaths, but also led to patient-centred improvements in self-care and QoL. This positive effect of mHealth on QoL was to be expected, given the empowerment of patients to improve their self-care combined with the clinical benefits obtained.

Importantly, the benefits of mHealth were consistent across several subgroups representing a range of real-world individuals with heart failure, making this strategy suitable to ensure equity of access to the best standard of care for most people with heart failure. Beyond the inclusion and exclusion criteria, there was no rigorous pre-screening protocol to identify patients who were suitable for enrolment. We consider the absence of such a protocol for pre-screening to be a strength of the HERMeS trial. The generous inclusion criteria would be expected to help recruit a wide range of patients reflective of real-world practice. Furthermore, the results of intraclass correlation analysis indicated no clinically meaningful sources of bias between centres in terms of individuals likely to respond to guideline-directed medical treatment and mHealth. Individuals with elevated vulnerability to adverse health outcomes a priori, such as those with frailty or low literacy or ICT skills, appeared to benefit from the mHealth tool, confirming findings from previous subanalyses.[28,34]

The HERMeS trial had some notable limitations, principally those that are typical of an unmasked study. No demographic data relating to ethnicity were recorded as this variable was not defined in electronic case report forms, so it was not possible to assess whether there was a relationship between ethnicity and implementation of mHealth. The trial did not include any prespecified collection of data related to harms, although no concerning features were reported spontaneously during the follow-up period. Given that we observed changes in heart failure medication use, future studies should include systematic collection of harms data as well as providing an opportunity to collect spontaneous reporting of such information. Incorporating mHealth required heart failure care teams to respond to a large number of alarms and initiate subsequent unplanned contacts to achieve good outcomes. Our protocol did not require the collection of data related to alarm response times and the associated specific actions on a patient or centre level, although such data will be important to understand how to optimally plan and implement mHealth programmes. Nor did we evaluate the effect of handling these alarms on workflow and staff-related factors such as staffing requirements, scheduling, and training, which would be essential in understanding each health centre's requirements for routine implementation. We also note that although our power calculation indicated the need to recruit 508 patients, the final full analysis set comprised data for a lower number (n=506). However, this did not appear to limit the clinical effect of mHealth intervention, with the primary and most secondary clinical objectives met. To minimise the risk of bias from elements such as the below-target sample, masked clinical endpoint adjudication was done by an independent committee. Additionally, the protocol allowed for local differences in standard of care in each centre according to best practice, which could have contributed to variations in data across the study population. To mitigate such potential effects, we attempted to standardise the minimum standards of care between the centres during follow-up. Clustering effects in this multicentre trial were another potential source of bias, but intraclass correlation coefficient values were uniformly low, suggesting minimal effects due to differences in performance or health-care models between centres (for example, in managing video consultations). Further studies could evaluate the factors that facilitate optimal mHealth delivery. Additionally, the COVID-19 pandemic hampered the development of the HERMeS study, particularly in terms of recruitment, but there was no requirement as determined by the trial steering committee and other institutions to modify the protocol. Specifically regarding heart failure pharmacotherapy, we emphasise that data on the use of sodium–glucose co-transporter 2 inhibitors and vericiguat could not be collected because they were not yet indicated as disease-modifying drugs for heart failure in clinical practice guidelines at the beginning of the study (May 15, 2018).[23]

In conclusion, in real-world individuals after a recent hospital admission due to heart failure decompensation, we found that implementing non-invasive telemedicine services based on mHealth combining teleintervention and telemonitoring showed efficacy in preventing fatal and non-fatal cardiovascular events. Future studies comparing non-invasive and invasive strategies in the early post-discharge period in the context of new pharmacotherapies could be useful to understand the role that each of these strategies can play in the follow-up of patients with heart failure. Studies to establish the full requirements of implementing mHealth for heart failure health-care teams are also warranted.

Contributors

SY contributed to study conception and design, project administration, data acquisition, investigations, methodology, supervision, data curation, formal analyses and interpretation, and manuscript drafting and critical revision

and editing. JC-C contributed to study conception and design, funding acquisition, project administration, data acquisition, investigations, methodology, supervision, data curation, formal analyses and interpretation, manuscript drafting and critical revision and editing, reviewing the manuscript for important intellectual content, and final approval of the version to be published. EC-M, EH, NJ-B, MCM, TS, PLl, CF, JMG-P, CC, ÁG-F, EMG-M, JLM-R, CS, EG-R, JN, JC, CF, and MF contributed to data acquisition, investigations, and manuscript drafting and critical revision. PM, FF, Jd-JB, and IZ-R contributed to clinical event adjudication, data curation, and manuscript drafting and critical revision. JMV-R, EV, DM, JP-J, and GC-S contributed to investigations and manuscript drafting and critical revision. CE contributed to study conception and design, project administration, data acquisition, investigations, methodology, supervision, data curation, formal analyses and interpretation, manuscript drafting and critical revision and editing, reviewing the manuscript for important intellectual content, and final approval of the version to be published. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. SY, JC-C and CE accessed and verified the data and had access to the raw data in the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this Article after de-identification (text, tables, figures, and appendices) are available after publication. To access the data, please email the principal investigator of the study, Josep Comín-Colet (josepcomin@gmail.com). The use of data will be allowed for specified, approved purposes and for meta-analysis with investigator support and with a signed data access agreement and after approval of a proposal. Access to statistical and analytical code documents can be provided to researchers who provide a methodologically sound proposal and whose use of the data has been approved. The protocol and statistical analysis plan are provided in appendix 2 and appendix 3.

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