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RESEARCH ARTICLE

Effects of an outpatient intervention comprising nurse-led non-invasive assessments, telemedicine support and remote cardiologists' decisions in patients with heart failure (AMULET study): a randomised controlled trial

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Aim Prevention of heart failure (HF) hospitalisations and deaths constitutes a major therapeutic aim in patients with HF. The role of telemedicine in this context remains equivocal. We investigated whether an outpatient telecare based on nurse-led non-invasive assessments supporting remote therapeutic decisions (AMULET telecare) could improve clinical outcomes in patients after an episode of acute HF during 12-month follow-up.

Methods and results In this prospective randomised controlled trial, patients with HF and left ventricular ejection fraction (LVEF) ≤49%, after an episode of acute HF within the last 6 months, were randomly assigned to receive either an outpatient telecare based on nurse-led non-invasive assessments ($n = 300$) (AMULET model) or standard care ($n = 305$). The primary composite outcome of unplanned HF hospitalisation or cardiovascular death occurred in 51 (17.1%) patients in the telecare group and 73 (23.9%) patients in the standard care group up to 12 months after randomization [hazard ratio (HR) 0.69, 95% confidence interval (CI) 0.48–0.99; $P = 0.044$]. The implementation of AMULET telecare, as compared to standard care, reduced the risk of first unplanned HF hospitalisation (HR 0.62, 95% CI 0.42–0.91; $P = 0.015$) as well as the risk of total unplanned HF hospitalisations (HR 0.64, 95% CI 0.41–0.99; $P = 0.044$).There was no difference in cardiovascular mortality between the study groups (HR 1.03, 95% CI 0.54–1.67; $P = 0.930$).

Conclusions AMULET telecare as compared to standard care significantly reduced the risk of HF hospitalisation or cardiovascular death during 12-month follow-up among patients with HF and LVEF ≤49% after an episode of acute HF.

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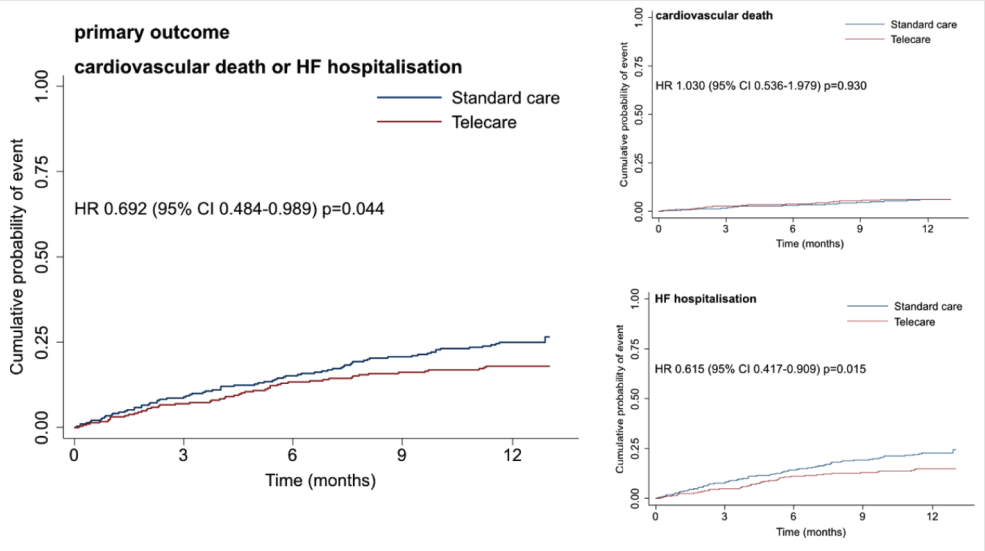
Graphical Abstract



Among patients with heart failure (HF) the AMULET telecare model, comprising nurse-led non-invasive assessments, telemedicine support and remote cardiologists' decisions, reduced the risk of the primary composite endpoint of cardiovascular death or HF hospitalisation and this effect was driven by a significant reduction in the risk of HF hospitalisations. CI, confidence interval; HR, hazard ratio.

Keywords Heart failure • Ambulatory care • Telecare • Heart failure hospitalisation

Introduction

Heart failure (HF) is a worldwide health burden.[1–3] Its prevalence in developed regions is estimated to be 1–2%, with even higher rates for some countries, such as China, the United States and Germany.[1,2] Prevention of recurrent HF hospitalisations is of particular relevance, as each successive event triggers the progression of heart damage, exacerbates HF symptoms, impairs quality of life, favours disability, and translates into high mortality among patients with HF.[1,4,5] HF hospitalisations account for the vast majority of direct and indirect costs associated with HF care and are anticipated to double within the next 20 years.[6,7]

There are premises that the application of telehealth solutions could lead to a reduction of HF hospitalisations and related unfavourable consequences for both individual patients and healthcare system. Home-based teleinterventions have been demonstrated to effectively reduce the risk of HF-related hospitalisations.[8–10] Until now, telecare systems based on remote transmission of parameters have been neither comprehensively investigated nor broadly implemented in clinical practice.

Information derived from non-invasive measurements (including body impedance) has proven their diagnostic and prognostic value.[11–14] In the pilot study, we have demonstrated that a 1-month care programme based on nurse-led ambulatory care including non-invasively haemodynamically-guided pharmacotherapy improved the functional status and quality of life of patients with HF after an episode of acute HF.[15] It is anticipated that telemedicine solutions based on such non-invasive measurements could add to the optimisation of a care of HF patients and translate into survival benefits, but available evidence is limited.

In the AMULET study, we aimed to investigate the effects of an outpatient telecare model based on nurse-led non-invasive assessments supporting remote therapeutic decisions (AMULET telecare) as compared to standard care on a composite outcome of unplanned HF hospitalisation or cardiovascular death during 12-month follow-up in patients after an episode of acute HF.

Methods

Study design

The AMULET trial was a multicentre, prospective, randomised, open-label, controlled, parallel group trial performed in Poland (ClinicalTrials.gov Identifier: NCT03476590). The rationale and study design have been published previously.[16] The trial was approved by the local ethics committee (no. 70/WIM/2016). The investigation conformed to the principles outlined in the Declaration of Helsinki and principles of Good Clinical Practice. Each study participant provided written informed consent to participate in the study.

Participants, recruitment and randomisation

Briefly, eligible patients had to be aged 18 years or older, with a left ventricular ejection fraction (LVEF) ≤49% (not older than 6 months at the time of randomisation), and at least one hospitalisation due to acute HF within 6 months prior to randomisation. Patients with any of the following conditions were excluded from the study: myocardial infarction, stroke, or pulmonary embolism within 40 days prior to randomisation, diagnosis of severe pulmonary diseases, chronic kidney disease (stage 5 and/or requiring dialysis), severe inflammatory disease, severe mental and physical disorders at any time (detailed inclusion and exclusion criteria are provided in online supplementary *Table S1*).[16]

The AMULET study was conducted in ambulatory settings in nine sites in Poland.[16] When the site was in the structure of the hospital performing procedures of invasive cardiology and procedures of cardiac surgery it was classified as 'high-reference/university clinic'. The sites in the structure of the hospitals not performing such procedures were recognized as 'district hospitals'. The outpatient clinics providing cardiology consultations but not being in the structure of any hospital were defined as 'outpatient specialist outpatient clinics'.

The study participants were randomly assigned in a 1:1 ratio to the intervention (telecare) or standard care groups. Randomisation was performed centrally using a computerised permuted block technique (random sequences of allowable block sizes of 4, 6 or 8).[16]

Study procedures and intervention

All study procedures have been presented in details in the design paper.[16]

In the intervention group (telecare), patients were exposed to seven outpatient visits performed by nurses in the nurse consulting space (named as ambulatory care point, ACP), during 12 months of follow-up according to a pre-defined schedule (online supplementary *Figure S1*).

According to the study protocol, the nurse was assigned the following tasks: (i) to assess the intensity of HF symptoms according to the New York Heart Association (NYHA) classification system, breathlessness, orthopnoea, nocturnal cough, wheezing, loss of appetite, palpitations, syncope, weight gain (>2 kg/week), peripheral oedema, ascites, and tachypnoea – using pre-defined questionnaires and other tools,[16] (ii) to perform the measurements with impedance cardiography (ICG)[12] and bioimpedance scale[17]; (iii) to provide the patient the recommendation formulated by the physician.[16] No treatment decisions were made by the nurse herself, while the remote consultations and final therapeutic decisions for each particular patient were realized by the assigned onsite cardiologist who had performed the first face-to-face recruitment visit.

Neither transmission of data from patients at home, contact with the study site, short text messages nor phone calls, were planned between scheduled visits in the study protocol. Each visit included the following stages (*Figure 1*):

(i) a nurse-led assessment of HF signs and symptoms with measurements of the following vital parameters at resting conditions: heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), thoracic fluid content (TFC), body mass (BM) and total body water (TBW), using ICG[12] and bioimpedance technique[17];
(ii) a transmission of aforementioned recorded parameters and clinical features to the telemedicine web service and its remote presentation to the cardiologist within the recommendation support module (RSM);
(iii) therapeutic decisions taken by a cardiologist based on available data from the patient delivered remotely and supported by RSM indications and subsequently sent back to the nurse who provided information about therapeutic decision to an individual patient and recommended to follow this advice.

In the control group (standard care), patients were advised to remain under the supervision of cardiologists and other physicians using the facilities available in the 'real-life' healthcare system based on current clinical needs. According to the study protocol, the role of the primary treating doctor was intact. The visits delivered during the study did not affect the services provided by the general practitioner or other specialists.

The key study assessments were performed at baseline (before the intervention was implemented) and at the last visit scheduled at 12 months (with a ± 30-day margin) for both study groups.

Applied technologies

Non-invasive haemodynamic assessments were performed using ICG (Cardioscreen 2000, Medis, Ilmenau, Germany) and body composition analysis (MC-418MA Composition Analyser, Tanita, Tokyo, Japan). The measurements were automatically transferred into the telemedicine web service, and the following parameters were available for therapeutic decision-making: HR, SBP, DBP, TFC, visit-to-visit change in TFC (ΔTFC), visit-to-visit change in BM (ΔBM) and visit-to-visit change in TBW (ΔTBW). Their values were presented within the RSM in relation to pre-defined alarms.

The physicians were instructed to interpret RSM indications according to the staging of alarms marked by the colours: white, green, yellow and red (*Figure 1*). The optimal range (white) and staged alarm ranges (green, yellow and red) were developed basing on current guidelines[1] and our previous experience in haemodynamic assessment. For example, if the TFC value fell within the red right-side alarm range, the patient was presumed to be heavily congested and recommended for an urgent in-person physician consultation within 2 h. This approach was applied from the second visit, when all seven parameters (including visit-to-visit changes) were available. The physicians were encouraged to report if their final recommendations were (or were not) in agreement with RSM alarms. The rationale and instruction on how to use RSM indications in therapeutic decisions have been presented in details in the design paper.[16] At the end of the visit, the patient was provided with final recommendations set remotely by the cardiologist in the telemedicine web service.[16]

According to the study protocol, the recommended modifications in therapy due to information obtained during the study visit by the nurse (questionnaires and measurements) were related only to therapies which were possible to be delivered in home settings. Therefore, they included only oral drugs.

Study outcomes

The primary outcome was a composite of the first unplanned HF hospitalisation or cardiovascular death assessed during 12-month follow-up after randomisation (with a ± 30-day margin).

Secondary outcomes included: (i) cardiovascular death, (ii) death due to HF worsening, (iii) all-cause death, (iv) the first unplanned HF hospitalisation, (v) the first unplanned cardiovascular hospitalisation, (vi) the first unplanned all-cause hospitalisation, (vii) a total number of unplanned HF hospitalisations (recurrent event analysis), (viii) days

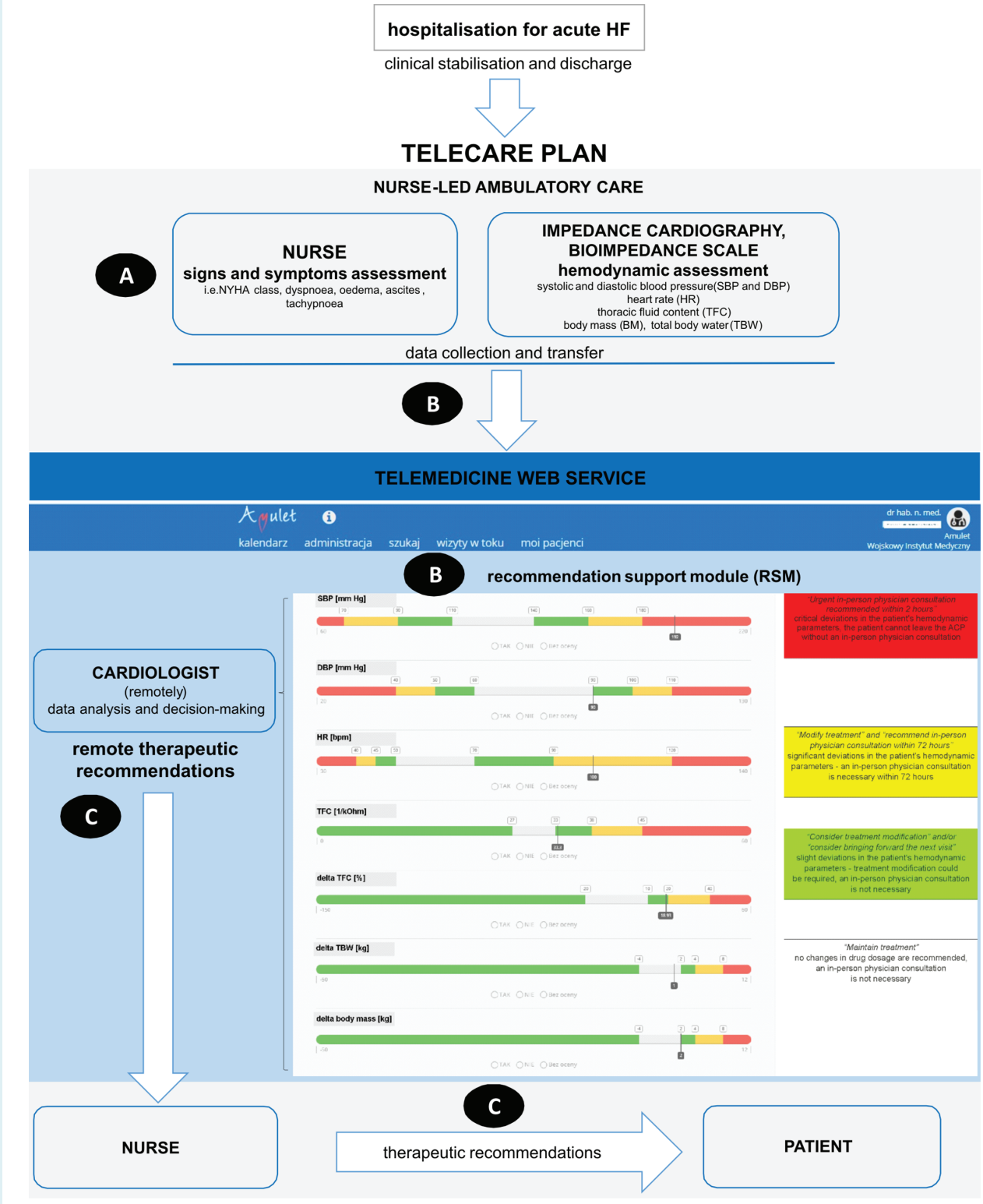


Figure 1 The AMULET telecare model: (*A*) a nurse-led assessment, (*B*) a transmission of the recorded parameters and clinical features to the telemedicine web service with presentation within the recommendation support module (RSM); (*C*) cardiologist remote therapeutic decisions.

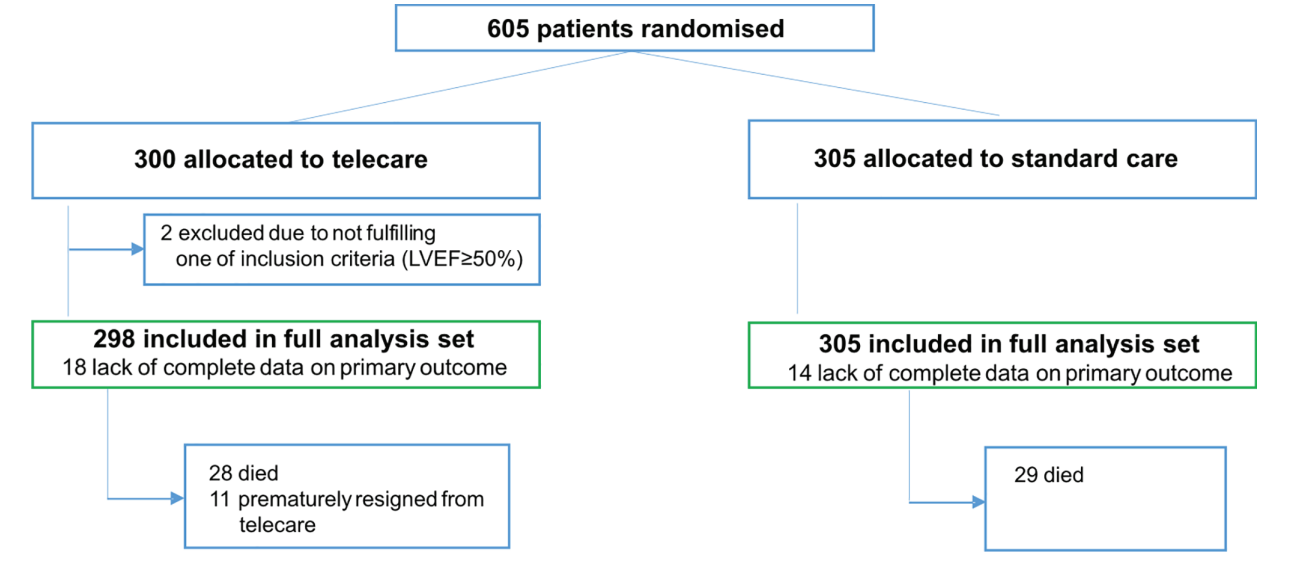


Figure 2 Study flow chart (intention to treat analysis). LVEF, left ventricular ejection fraction.

lost due to HF hospitalisations or death for any cause. All secondary outcomes were assessed during the 12-month follow-up after randomisation (with a ± 30-day margin).

All hospitalisations and causes of deaths were adjudicated by a blinded independent Endpoint Adjudication Committee (online supplementary *Table S2*[16]) using pre-specified criteria (online supplementary *Table S3*[16]). For patients who died, the number of days lost between the date of death and the date of intended follow-up (395/396 days) plus the number of days spent in hospital due to HF hospitalisations were calculated.

Statistical analysis

The analyses were done according to the pre-specified statistical analysis plan.

Sample size calculation

It was anticipated to expect the rate of 30% for a primary outcome in the standard care group during the 12-month follow-up (control group).[16] It was assumed that the AMULET telecare would result in a risk reduction of a primary outcome by 33%. As a consequence, taking into account a two-sided alpha level of 0.05 to control type I error and 80% power to detect the aforementioned effect of an intervention, a sample size was estimated of 296 subjects for each study arm.

Statistical analyses for between-group comparisons

The Stata software (version 16.1, StataCorp LLC, College Station, TX, USA) was used to perform statistical analyses. *P*-values <0.05 (two-sided) were considered significant for all analyses.

Descriptive statistics included medians and interquartile ranges for continuous variables, as well as frequencies and percentages for categorical variables. The between-group differences in baseline values of continuous variables were tested using the independent Student's *t*-test (with the Satterthwaite approximation for non-homogeneous variances) or the Mann–Whitney U test (for variables with skewed distribution). The between-group differences in proportions of categorised variables were tested using the Pearson's chi-squared test, or the Fisher's exact test in cases of less than five expected frequencies in each cell of a contingency table.

Statistical analyses for the effect of an intervention on study outcomes

The efficacy analysis was performed within the full analysis set which consisted of subjects who were randomised, assigned accordingly to respective study arm and completed a recruitment visit, according to the intention-to-treat principle.

In the time-to-first event models, Cox-proportional hazard regression with Efron's method of handling ties was used to define hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) for the magnitude of the treatment effect (telecare vs. standard care). The proportionality of hazards assumption was checked using the Schoenfeld residuals-based test. The Kaplan–Meier method was used to derive the curves reflecting the proportions of patients being free of pre-defined endpoints at certain timepoints. The patients, for whom no information was available after the recruitment visit, were censored on 'day of the recruitment visit +1 day'. This rule was applied to both telecare and standard care groups in the primary endpoint analysis and all other 'time-to-event' analyses. Moreover, patients in the telecare group, for whom no information was available after one of the ambulatory visits ('day X'), were censored on 'day X'.

The Andersen–Gill model (the extended Cox model, which is formulated in terms of increments in the number of events along the time line[18]), was used for the recurrent time-to-event analysis for a total number of HF hospitalisations.

The difference in number days lost due to HF hospitalisations or death for any cause was tested using the Mann–Whitney U test.

Additional analyses and models

The effect of AMULET telecare as compared to standard care on the risk of the primary outcome was also estimated in a multivariable model with the following co-variables: gender (males vs.

Table 1 Baseline characteristics of the study patients

Variables	All patients	Patients in the telecare arm ($n = 298$)	Patients in the standard care arm ($n = 305$)
Female sex	129 (21)	64 (21)	65 (21)
Age, years	67 (14)	67 (16)	67 (13)
Age ≥ 65 years	353 (59)	174 (58)	179 (59)
Systolic blood pressure, mmHg	122 (21)	123 (23)	122 (20)
Diastolic blood pressure, mmHg	76 (11)	76 (12)	76 (10)
Heart rate, bpm	72 (13)	71 (13)	73 (13)
BMI, kg/m^2	28 (7)	28.0 (7)	29 (7)
Obesity (BMI ≥30 kg/m^2)	353 (60)	183 (63)	170 (58)
LVEF, %	32 (15)	32 (15)	33 (16)
LVEF <40%	412 (70)	210 (72)	202 (68)
Ischaemic aetiology of HF	373 (62)	178 (60)	195 (64)
NYHA functional class			
I	63 (11)	28 (9)	35 (12)
II	390 (65)	188 (63)	202 (67)
III	144 (24)	80 (27)	64 (21)
IV	3 (1)	1 (<1)	2 (1)
Comorbidities			
Previous myocardial infarction	261 (43)	122 (41)	139 (46)
Previous coronary artery percutaneous angioplasty	250 (42)	120 (40)	130 (43)
Previous coronary artery bypass grafting	76 (13)	35 (12)	41 (13)
Previous stroke	60 (10)	36 (12)	24 (8)
Hypertension	370 (61)	196 (66)	174 (57)
Diabetes	232 (39)	109 (37)	123 (40)
Atrial fibrillation or flutter	333 (55)	171 (53)	162 (58)
Chronic kidney disease	132 (22)	64 (22)	68 (22)
Chronic obstructive pulmonary disease	69 (11)	29 (10)	40 (13)
Smoking			
Never	203 (34)	106 (36)	97 (32)
Past	313 (52)	156 (53)	157 (51)
Current	86 (14)	35 (12)	51 (17)
Pharmacotherapy			
Angiotensin-converting enzyme inhibitor	434 (72)	216 (73)	218 (72)
Angiotensin receptor blocker	33 (6)	21 (7)	12 (4)
Angiotensin receptor–neprilysin inhibitor	12 (2)	8 (3)	4 (1)
Mineralocorticoid receptor antagonist	400 (67)	205 (69)	195 (64)
Beta-blocker	552 (92)	276 (93)	276 (91)
Loop diuretic	499 (83)	244 (82)	255 (84)
Digitalis glycosides	69 (12)	37 (13)	32 (11)
Devices			
Implantable cardioverter-defibrillator	121 (20)	68 (23)	53 (17)
Cardiac resynchronisation therapy	69 (11)	37 (12)	32 (10)
Laboratory test results			
Haemoglobin, g/dL	14.0 (3.0)	14.0 (3.0)	14.0 (3.0)
Anaemia[a]	132 (23)	63 (22)	69 (24)
eGFR, 60 mL/min/1.73 m^2	62 (32)	61 (32)	63 (31)
eGFR < 60 mL/min/1.73 m^2	265 (47)	136 (49)	129 (45)
Days between discharge for most recent HF hospital admission and recruitment			
≤30 days	277 (49)	137 (49)	140 (49)
>30 days	290 (51)	144 (51)	146 (51)
Centre reference			
High-reference or university clinic	409 (68)	202 (68)	207 (68)
District hospital or outpatient specialist clinic	194 (32)	96 (32)	98 (32)

Data are presented as median (interquartile range as equal to the difference between upper and lower quartiles, IQR) and *n* (%). Percentages might not add to 100% because of rounding.

BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

[a]Anaemia defined as haemoglobin level <13 g/dL in men, and <12 g/dL in women.

Table 2 Primary and secondary outcomes

Outcome	Telecare arm ($n = 298$)	Standard care arm ($n = 305$)	HR (95% CI)	*P*-value
Primary outcome				
First unplanned HF hospitalization or cardiovascular death[a], *n* (%)	51 (17.1)	73 (23.9)	0.69 (0.48–0.99)	0.044
Secondary outcomes				
Death for any cause[a], *n* (%)	28 (9.4)	29 (9.5)	0.99 (0.59–1.67)	0.983
Cardiovascular death[a], *n* (%)	18 (6.0)	18 (5.9)	1.03 (0.54–1.98)	0.930
Death due to worsening HF[a], *n* (%)	10 (3.4)	14 (4.6)	0.74 (0.33–1.66)	0.461
First unplanned hospitalization for any cause[a], *n* (%)	69 (23.2)	90 (29.5)	0.74 (0.56–1.05)	0.092
First unplanned cardiovascular hospitalization[a], *n* (%)	62 (20.8)	80 (26.2)	0.78 (0.56–1.08)	0.137
First unplanned HF hospitalization[a], *n* (%)	41 (13.8)	66 (21.6)	0.62 (0.42–0.91)	0.015
Unplanned HF hospitalisations, *n*	62	97	0.64 (0.41–0.99)	0.044
Days lost due to HF hospitalisations or death for any cause, mean ± SD	25.8 ± 79.6	24.8 ± 74.4	-	0.101

CI, confidence interval; HF, heart failure; HR, hazard ratio; SD, standard deviation.
[a]Number (%) of patients with an event.

females), estimated glomerular filtration rate (eGFR) as per Modification of Diet in Renal Disease (MDRD) formula (<60 mL/min/1.73 m^2 vs. ≥60 mL/min/1.73 m^2), LVEF (<40% vs. 40–49%), age (≥65 years vs. <65 years), time between enrolment and discharge from an index hospitalisation [early (≤30 days) vs. late (>30 days)] and centre of reference (high-reference/university clinics vs. district hospitals/outpatient specialist clinics).

For the primary and secondary outcomes (time-to-first event models), a sensitivity analysis with use of the Fine and Gray method[19] was done to account for the presence of the competing risk of death.

As the management and follow-up of patients might have been affected by the coronavirus disease 2019 (COVID-19) pandemic,[20,21] an additional sensitivity analysis for the primary and secondary outcomes (time-to-first event models), censoring patients at the date when the first COVID-19 patient was reported in Poland (4 March 2020), was also performed.

For the primary outcome, the treatment effect was estimated among seven pre-specified subgroups: (i) males vs. females, (ii) eGFR as per MDRD formula <60 mL/min/1.73 m^2 vs. ≥60 mL/min/1.73 m^2), (iii) LVEF <40% vs. 40–49%, (iv) ischaemic HF vs. non-ischaemic HF, (v) age <65 years vs. ≥65 years, (vi) early (≤30 days) vs. late (>30 days) time between enrolment and discharge, and (vii) level of reference for recruiting centres (high-reference/university clinics vs. district hospitals/outpatient specialist clinics).

Results

Recruitment and patient flow

Between 6 March 2018 and 26 September 2019, 605 patients at nine sites in Poland were recruited and randomly assigned to receive either the AMULET telecare ($n = 300$) or standard care ($n = 305$). Four hundred and ten subjects were enrolled in four high-reference/university clinics (203 assigned to telecare and 207 assigned to standard care), 83 subjects were enrolled in two district hospitals (40 assigned to telecare and 43 assigned to standard care) and 112 subjects were enrolled in three outpatient specialist clinics (57 assigned to telecare and 55 assigned to standard care).

At the recruitment visit, two patients in the intervention group due to LVEF >50% were excluded from the intention-to-treat population. During the study execution, 11 patients in the intervention group (3.7%) prematurely resigned from ambulatory visits with telecare, but did not withdraw their consent to be further followed up (*Figure 2*). Finally, a total of 1742 ambulatory visits with the AMULET telecare were performed in the intervention group (on average 5.85 visits per patient for all allocated to the intervention), which corresponded to 86% of scheduled visits. Based on the data delivered from the Polish National Health Fund (only a summary report was available due to legal reasons), there were 1670 visits performed (on average 5.48 visits per patient) in public healthcare system in the standard care group.

In the telecare group, a total number of 396 yellow and 77 red RSM alarms occurred, including 59 yellow and 11 red alarms for SBP, 33 yellow and 3 red alarms for DBP, 86 yellow and 11 red alarms for HR, 76 yellow and 18 red alarms for TFC, 62 yellow and 13 red alarms for ΔTFC, 27 yellow and 10 red alarms for ΔTBW, 53 yellow and 11 red alarms for ΔBM. The overall agreement of the final physician remote recommendations with yellow alarms was 79% and with red alarms was 86%.

Data regarding the occurrence (or not) of a primary endpoint within the full intended duration of the protocol follow-up was available for 280 (94.0%) patients in the telecare group and for 291 (95.4%) patients in the standard care group. Eighteen subjects (2.9%) were lost to follow-up immediately after recruitment visit (8 in the telecare group and 10 in the standard care group). For the remaining 14 subjects (10 in the telecare group and 4 in the standard care group) the median of follow-up was 36 days (range 7–280 days).

The information on first unplanned hospitalisation, unplanned cardiovascular hospitalisation and HF hospitalisation within the full intended duration of the protocol follow-up was not completed

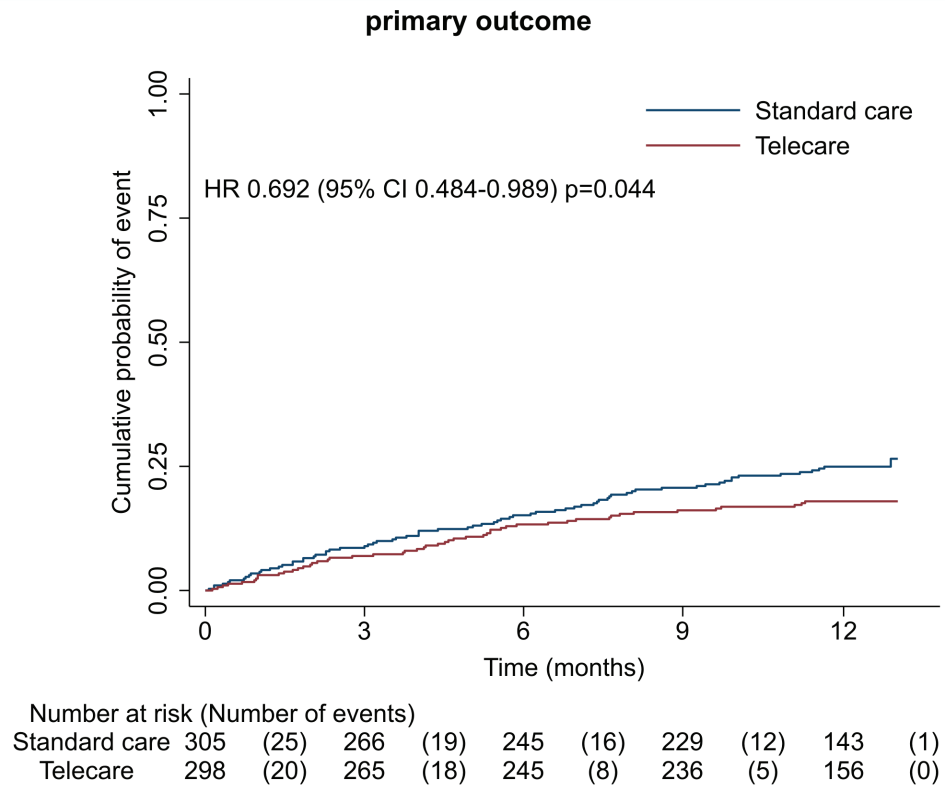


Figure 3 Primary outcome. CI, confidence interval; HR, hazard ratio.

for 16 (5.4%), 16 (5.4%) and 18 (6.0%) patients in the telecare group and for 14 (4.6%), 14 (4.6%) and 14 (4.6%) patients in the standard care group. All-cause mortality data were available for all patients participating in the trial, whereas the cause of death was not identified among 6 (2.0%) patients in the telecare group and for 6 (2.0%) patients in the standard care group.

Baseline characteristics

The baseline characteristics and applied medications were balanced between both study groups, apart from a slightly higher prevalence of hypertension in the telecare group (*Table 1*).

Primary endpoint

The primary endpoint occurred in 51 of 298 patients (17.1%, 41 first HF hospitalisations and 10 cardiovascular deaths) in the telecare group and in 73 of 305 patients (23.9%, 66 first HF hospitalisations and 7 cardiovascular deaths) in the standard care group, demonstrating a 31% reduction in the risk of first unplanned HF hospitalisation or cardiovascular death during the 12-month follow-up due to the AMULET telecare (HR 0.69, 95% CI 0.48–0.99; $P = 0.044$) (*Table 2* and *Figure 3*).

Secondary endpoints

The first unplanned HF hospitalisation occurred in 41 (13.8%) patients in the telecare group and in 66 (21.6%) patients in the standard care group (HR 0.62; 95% CI 0.42–0.91; $P = 0.015$) (*Table 2* and *Figure 4F*). There was no difference in the rates of either unplanned cardiovascular (*Figure 4E*) or unplanned all-cause hospitalisations (*Figure 4D*) between the study groups (all non-significant). There was no difference in either all-cause (*Figure 4A*), cardiovascular (*Figure 4B*) or HF-related (*Figure 4C*) mortality between the study groups (all non-significant, *Table 2*).

The Schoenfeld residual-based tests indicated that the proportionality of hazards assumptions was met for all Cox regression models performed in the analysis of primary and secondary outcomes ($P > 0.05$).

In the model of recurrent time-to-event analysis, 62 unplanned HF hospitalisations occurred in the intervention group and 97 in the standard care group (HR 0.64, 95% CI 0.41–0.99; $P = 0.044$) (online supplementary *Figure S2*).

The number of days lost to HF hospitalisations and all-cause death was similar for both groups (mean: 25.8 vs. 24.8 days; $P = 0.101$).

Additional analyses and models

The risk of a primary endpoint was reduced in the telecare as compared to the standard care group also in the model adjusted for co-variables (HR 0.67, 95% CI 0.46–0.99; $P = 0.045$).

In the sensitivity analysis accounting for the competing risk of death, the effect of telecare as compared to standard care

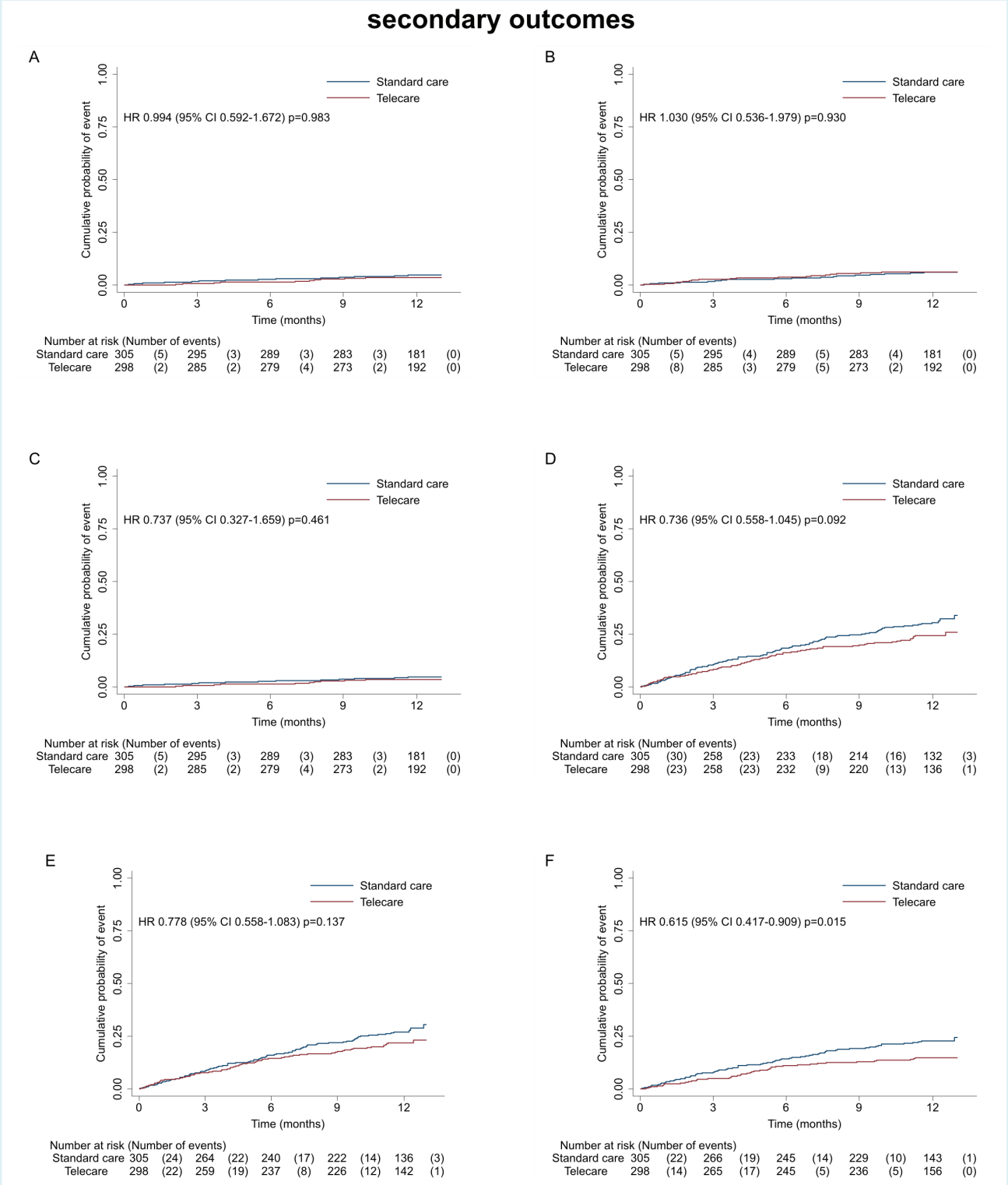


Figure 4 Time-to-event secondary outcomes: (*A*) death for any cause, (*B*) cardiovascular death, (*C*) death due to worsening heart failure, (*D*) first unplanned all-cause hospitalisation, (*E*) first unplanned cardiovascular hospitalisation, (*F*) first unplanned heart failure hospitalisation. CI, confidence interval; HR, hazard ratio.

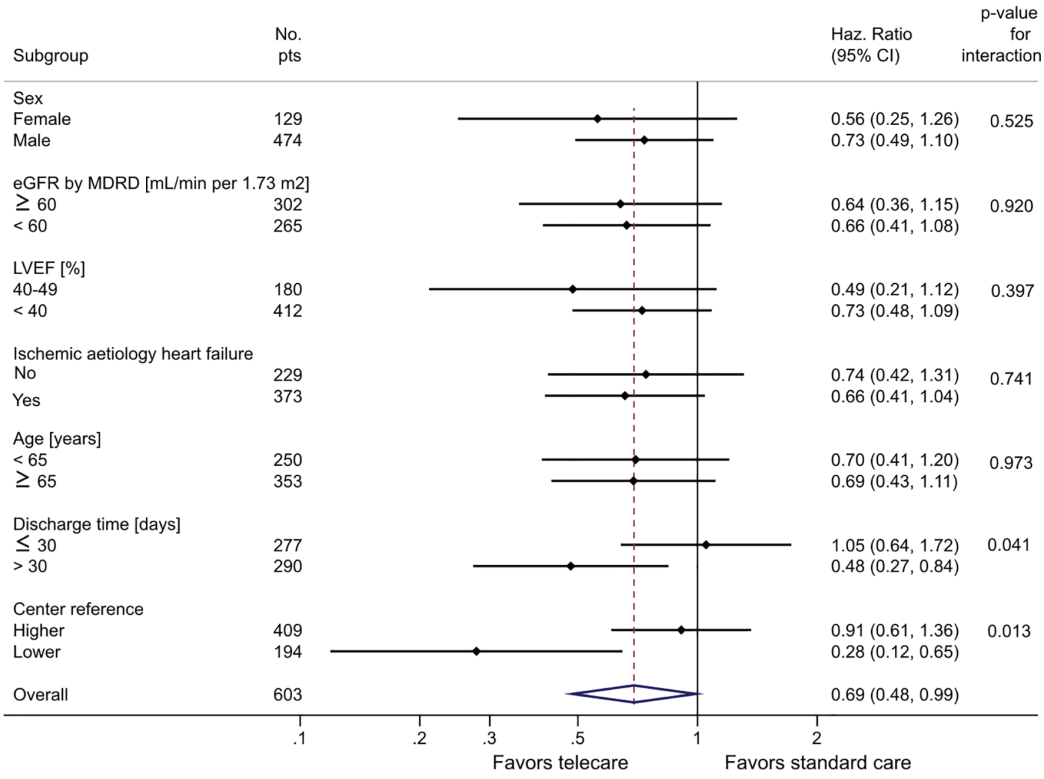


Figure 5 Forest plot for the primary outcome (first unplanned heart failure hospitalisation or cardiovascular death) by subgroup in the intention-to-treat population. CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease.

on the risk of primary outcome was also significant [subdistribution hazard ratio (SHR) 0.70, 95% CI 0.48–0.99; $P = 0.049$], as well as for the risk of first unplanned HF hospitalisation (SHR 0.61, 95% CI 0.42–0.91; $P = 0.014$) (online supplementary *Table S4*).

Out of 121 scheduled visits which occurred during the COVID-19 pandemic, 78 visits were executed onsite according to the study protocol, 35 visits were postponed and were executed as onsite visits (with median delay of 57 days, maximum of 122 days), while only remaining 8 visits were substituted by phone calls. In the pre-COVID-19 sensitivity analysis, 49 primary endpoints occurred in the telecare group and 70 in the standard care group, demonstrating a 31% reduction in the risk of first unplanned HF hospitalisation or cardiovascular death due to the AMULET telecare (HR 0.69, 95% CI 0.48–0.99, $P = 0.048$). For the secondary outcomes, the risk of first unplanned HF hospitalisation was reduced by 37% (HR 0.63; 95% CI 0.42–0.93; $P = 0.022$) (online supplementary *Table S4*). There was no difference noted for other time-to-event secondary outcomes.

In the pre-specified subgroup analyses being exploratory in their nature, the effect of the AMULET telecare on the primary composite endpoint was consistent across pre-specified subgroups; however, there was a pattern that patients discharged >30 days before enrolment and patients under the care of lower reference centres could potentially benefit more (*Figure 5*).

Discussion

In this prospective randomised controlled trial, we demonstrated that the outpatient AMULET telecare model based on nurse-led non-invasive assessments supporting remote therapeutic decisions reduced the risk of first unplanned HF hospitalisation or cardiovascular death by 31% in patients after an episode acute HF. This effect was driven by a significant reduction in the risk of first unplanned HF hospitalisation (by 38%) without any effect on cardiovascular mortality. Importantly, also the total number of all unplanned HF hospitalisations was reduced by 36% due to this telemedicine intervention.

A significant heterogeneity in the methodological approach of other already published telemedicine models limits the possibility of direct comparisons with our telecare model. The nurse-coordinated disease management programme in patients discharged from hospital after HF decompensation was tested in the INH study.[22] HF nurses, supervised by a cardiologist, performed telephone standardized inquiries about patients' general health and well-being, addressed their individual problems, provided education and pursued networking of healthcare providers and caregivers. In comparison with usual care this model was neutral for the primary endpoint (a composite of time to all-cause death or rehospitalisation) but mortality risk and surrogates of well-being improved significantly.[22] The telemedicine models of care focused on home

monitoring presented different results regarding the effects on primary endpoints.[9,23–28] For example, the Tele-HF and WISH studies did not demonstrate benefits[25,26] while in the TIM-HF2 trial the use of remote patient management reduced the percentage of days lost to unplanned cardiovascular hospitalisations and all-cause mortality.[9]

The AMULET telecare provided evidence regarding the implementation of telemedicine solutions used by nurses in an ambulatory care for HF patients with a history of acute HF hospitalisation. The AMULET telecare model uses a network of ambulatory centres led by nurses who monitor different vital signs using different technologies, and co-operate in a remote manner with a cardiologist who provides feedback and treatment recommendations based on the acquired data. The AMULET concept might be combined with home telemonitoring solutions of proven clinical value (home telemonitoring[9] and telerehabilitation[29]) in a complex telecare system for HF patients.

The benefits of the AMULET telecare have been demonstrated in a population of patients with HF who seem to be stable and have a relatively low risk of cardiovascular death during 12-month follow-up (6% in the standard care arm), which was similar to other trial cohorts with stable patients with HF (PARADIGM-HF[30] 7%, DAPA-HF[31] 8%, EMPEROR-Reduced[32] 8%, TIM-HF2[9] 8% for placebo/control arms) and much lower than in other trials with HF (e.g. AFFIRM-AHF[33] 16%, SOLOIST-WHF[34] 13%, VICTORIA[35] 14% for placebo/control arms). In general, the majority of patients received guideline-recommended life-saving therapies (80% angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor–neprilysin inhibitor, 92% beta-blocker, 67% mineralocorticoid receptor antagonist). However, all of them had a history of HF hospitalisation, which identifies patients with a high risk of recurrent HF hospitalisations.[1,3,4,7] Indeed, the risk of HF hospitalisation or cardiovascular death in the AMULET study was 24%, and was higher than in other trials with patients with stable HFrEF (PARADIGM-HF[30] 12%, DAPA-HF[31] 15%, EMPEROR-Reduced[32] 21% for placebo/control arms), but still lower than in trials where patients were recruited shortly after being stabilised (AFFIRM-AHF[33] 47%, SOLOIST-WHF[34] 40%, VICTORIA[35] 30% for placebo/control arms). Interestingly, in the exploratory (but pre-specified) subgroup analyses, those who were recruited for the AMULET study benefited more if the time between the recent HF hospitalisation and the recruitment for the study was longer. Determination of the criteria of patient selection for the AMULET intervention may be needed in future studies.

Because of the high rate of mortality, rehospitalisation, poor quality of life and substantial costs, significant efforts should be made to improve the care of HF patients in outpatient settings. The primary unmet needs are resource shortages and the lack of an appropriate and consistent way to prevent HF decompensation.[36] The AMULET telecare model was created to address these challenges and was built upon the evidence from previous studies and our own experience.[11–14,18] Haemodynamic profiling by ICG has been demonstrated to be practical in differentiating the causes of dyspnoea,[11] predicting HF decompensation[12] or increased risk of death,[13] while bioimpedance analysis of total body composition has also been shown to provide additional value in determining volaemic status in HF.[14]

Prior studies on post-discharge programmes have demonstrated benefits in reducing rehospitalisation in HF patients.[37,38] The feasibility, cost-effectiveness and clinical efficacy of nurse care is also backed by solid evidence.[39,40] The AMULET telemedicine web service, which facilitates cardiologist teleconsultations for patients visiting ACPs, adds value to standard nurse care. Another advantage is the RSM, which enables tailoring pharmacotherapy to a patient's individual haemodynamic profile.

Study limitations

We need to acknowledge an open design of the trial. Importantly, it is worthy to be mentioned that the intervention was a combination of several elements (a nurse-led assessment, a transmission of the recorded parameters and clinical features to the telemedicine web service and cardiologist remote therapeutic decision), and that the observed benefits are due to the implementation of all of them. Hence, *a priori* it is not possible to specifically attribute the observed effects to any of them. It also cannot be ruled out that the missing data on a cause of death and cause of hospitalisations, though balanced between groups, could potentially influence the results. However, the post-hoc sensitivity analysis (online *supplementary material*) was consistent with the main analysis. The underrepresentation of women should also be considered.

Additionally, our study is one of the first randomised prospective clinical telemedicine trials that may have been affected by the COVID-19 pandemic. In the first wave of the COVID-19 pandemic in Poland (April–June 2020), the visit plan pre-specified by the study protocol was modified (postponed onsite visits or phone calls). However, the pre-specified pre-COVID-19 sensitivity analysis, which excluded the impact of the COVID-19 pandemic on the follow-up, was consistent with the main analysis and confirmed the significant benefit of the AMULET intervention on the primary endpoint.

Conclusions

Among patients with HF and LVEF ≤49% after an episode of acute HF occurring within 6 months prior to enrolment, the AMULET telecare as compared to standard care reduced the risk of the primary composite endpoint of cardiovascular death or first unplanned HF hospitalisation, and this effect was driven by a significant reduction in the risk of first unplanned HF hospitalisation with no apparent effect on cardiovascular mortality (*Graphical Abstract*).

Supplementary Information

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

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