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STUDY DESIGN

Rationale and design of the AMULET study: A new Model of telemedical care in patients with heart failure

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Abstract

Aims Heart failure (HF) is characterized by high mortality and hospital readmission rates. Limited access to cardiologists restricts the application of guideline-directed, patient-tailored medical therapy. Some telemedicine solutions and novel non-invasive diagnostic tools may facilitate real-time detection of early HF decompensation symptoms, prompt initiation of appropriate treatment, and optimal management of medical resources. We describe the rationale and design of the AMULET trial, which investigates the effect of comprehensive outpatient intervention, based on individualized haemodynamic assessment and teleconsultations, on cardiovascular mortality and unplanned hospitalizations in HF patients.

Methods and results The AMULET trial is a multicentre, prospective, randomized, open-label, and controlled parallel group trial (ClinicalTrials.gov Identifier: NCT03476590). Six hundred and five eligible patients with HF (left ventricular ejection fraction ≤49%, at least one hospitalization due to acute HF decompensation within 6 months prior to enrolment) were randomly assigned in a 1:1 ratio to either an intervention group or a standard care group. The planned follow-up is 12 months. The AMULET interventions are performed in ambulatory care points operated by nurses, with the remote support of cardiologists. The comprehensive clinical evaluation comprises measurements of heart rate, blood pressure, body mass, thoracic fluid content, and total body water. A recommendation support module based on these objective parameters is implemented in remote therapeutic decision-making. The primary complex endpoints are cardiovascular mortality and unplanned HF hospitalization.

Conclusions The AMULET trial will provide a prospective assessment of the effect of comprehensive ambulatory intervention, based on telemedicine and haemodynamically guided therapy, on mortality and readmissions in HF patients.

Keywords Heart failure; Outpatient care; Impedance cardiography; Telemedicine; Readmission

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Introduction

Heart failure (HF) is characterized by high morbidity and mortality, poor quality of life, and frequent hospitalizations. Its prevalence in the European population is estimated to be 0.4% to 2%.[1] In the United States, HF affected 5.7 million adults in 2012, and this is expected to rise to 8.4 million by 2030.[2,3] Hospitalizations account for more than half of the direct and indirect costs associated with HF.[4–6] The rate of readmission for HF deterioration is approximately 10% at 30 days after the initial hospitalization, increasing to 40% within 6 months.[1,7,8] Each successive HF readmission worsens the prognosis of the patient.[9,10]

Some telemedicine solutions have been successfully tested for their ability to provide real-time detection of early HF decompensation signs and symptoms and prompt initiation of appropriate treatment.[11,12] Overall, the results of telemedicine trials in HF are not consistently positive, although the majority of the evidence is in favour of a beneficial effect with regard to aspects such as self-care, overall mortality and HF-related hospitalizations.[12–21]

An effective telecare programme should consider the potential of telemedicine to better manage medical resources. The limited access of patients to ambulatory cardiologists restricts the application of the most important aspects of optimal comprehensive care: frequent assessment of clinical state, guideline-directed and patient-tailored medical therapy, regular reinforcement of patient education and advanced care planning.[1,22,23] In the AMULET project, we created ambulatory care points (ACP) aimed to reduce the involvement of cardiologists in outpatient care to that of only necessary activities. While replacing in-person physician contact with teleconsultation, we provided high-quality patient assessment by implementing modern non-invasive diagnostic tools, such as impedance cardiography (ICG) monitoring and body composition analysis. The ACP is operated by a trained nurse, and the comprehensive clinical evaluation of patients comprises measurements of heart rate, blood pressure, oxygen saturation, body mass, thoracic fluid content, and total body water. The increased emphasis on the patient's water status is justified by the fact that congestion is the main cause of worsening HF, and early diagnosis of fluid retention seems to be crucial in the prevention of unplanned HF hospitalization.[1]

As many as half of all patients discharged from hospital after acute HF decompensation may be insufficiently decongested, which increases the risk of haemodynamic collapse soon after discharge.[9,24] Therefore, the AMULET follow-up visit plan is intended to intensify care early after discharge and to maintain the patient in a stable condition during further visits. Complete clinical data are entered into a telemedicine web service, which includes remote decision-making by a cardiologist. Additionally, to optimize and adjust pharmacotherapy to a patient's individual haemodynamic profile, we also implement a recommendation support module based on objective haemodynamic parameters.

The choice of bioimpedance method was based on previous studies and our own experience. ICG was demonstrated to be of practical use in differentiating the causes of dyspnoea in emergency settings,[25] predicting HF decompensation[26] and identifying HF patients with higher defibrillation thresholds[27] or increased risk of death.[28] We also demonstrated that patients with acute decompensated HF and higher thoracic fluid content (TFC), in comparison with those with lower TFC values, presented with greater symptom severity in terms of NYHA (New York Heart Association) functional class, higher N-terminal pro-brain natriuretic peptide levels and lower left ventricular ejection fraction (LVEF).[29] Moreover, the results of the observational pilot study that preceded this randomized controlled trial showed that a 1 month care programme involving nurse-led ACPs equipped with bioimpedance devices improved the functional status and well-being of patients.[30] Bioimpedance analysis of total body composition has also been shown to provide additional value in determining volaemic status in different clinical settings.[31,32] We recognized its additional value for patients with dominant right ventricular dysfunction, in which pulmonary fluid may be normal even in the presence of massive ascites and peripheral oedema. ICG has been shown to have high intra-individual reproducibility, especially with regard to TFC. For example, in stable populations with coronary artery disease, its mean intra-day difference was 2.0%.[33] The stability of bioelectrical impedance scale measurements has also been proven. In healthy subjects, the estimated error of measurement for body mass was about 0.5 kg, and that of total body water (TBW) was approximately 1.0%.[34]

The main objective of this study is to assess the influence of the AMULET intervention on cardiovascular mortality and unplanned hospitalizations in HF patients in comparison with standard care. The effects on other clinical outcomes (all-cause mortality, mortality due to HF, and unplanned cardiovascular and all-cause hospitalizations), functional class, quality of life, and required medication will also be evaluated.

Study design

The AMULET trial is a multicentre, prospective, randomized (1:1), open-label, controlled, parallel group trial (ClinicalTrials.gov Identifier: NCT03476590). The AMULET Trial Steering Committee (TMS, see Appendix A) and principal investigators of each site designed the trial and wrote the study protocol. The study is guided by the principles of Good Clinical Practice (GCP) in accordance with the Declaration of Helsinki (1996) and has been approved by the local Ethics Committee. Each study participant provided written informed consent before the commencement of any trial-related procedures.

Patient assignment to study groups and randomization

Six hundred and five eligible patients meeting all the inclusion and none of the exclusion criteria (*Table 1*) were recruited to the study between March 2018 and September 2019 and randomly assigned in a 1:1 ratio to either an intervention group or a standard care group. Randomization was performed centrally using a computerized permuted block

Table 1 Inclusion and exclusion criteria in AMULET study

Inclusion Criteria
1. Age >18 years
2. HF with LVEF* ≤49%
3. At least one hospitalization due to acute HF decompensation** within 6 months prior to enrolment
4. Clinical presentation of the aforementioned acute HF decompensation in NYHA class III-IV
Exclusion Criteria
1. Cardiogenic shock
2. Myocardial (STE-ACS/NSTE-ACS) infarct as the main cause of hospitalization within 40 days prior to recruitment
3. Stroke within 40 days prior to recruitment
4. Cardiac surgery within 90 days prior to recruitment
5. Elective cardiac surgery (or any other high-risk surgery) planned within the next 90 days
6. Pulmonary embolism within 40 days prior to recruitment
7. Severe pulmonary diseases, including chronic obstructive pulmonary disease (stage C/D), uncontrolled asthma and pulmonary hypertension (WHO class III-IV)
8. Chronic kidney disease (stage 5 and/or requiring dialysis)
9. Severe inflammatory disease as the main cause of hospitalization, including pneumonia, sepsis and tuberculosis
10. Severe mental and physical disorders
11. Life expectancy of less than 12 months in the opinion of the physician due to reasons unrelated to HF
12. Patients who are currently enrolled in or who have completed studies involving the use of investigational devices or drugs within 30 days prior to enrolment in this study, or other cases in which the patient is receiving other investigational agents
13. Pregnancy
14. Refusal to participate

HF, heart failure; NSTE-ACS, no ST Elevation Acute Coronary Syndrome; NYHA, New York Heart Association; STE-ACS, ST Elevation Acute Coronary Syndrome; WHO, World Health Organization.

*LVEF determined using echocardiography, radionuclide angiography or cardiac magnetic resonance imaging documented up to 6 months before enrolment will be accepted.

**Acute HF decompensation will be diagnosed in cases of rapid (previous 28 days) onset or change in signs or/and symptoms of HF (shortness of breath/dyspnoea on exertion or at rest, orthopnoea, [paroxysmal] nocturnal dyspnoea, pulmonary oedema/congestion, peripheral oedema, hepato-jugular reflux and/or raised jugular venous pressure) associated with myocardial dysfunction (confirmed by cardiac imaging or/and elevated plasma N-terminal pro B-type natriuretic peptide), requiring specific treatment with IV diuretics, IV vasodilators and/or IV inotropes (excluding digoxin) in a hospital setting.

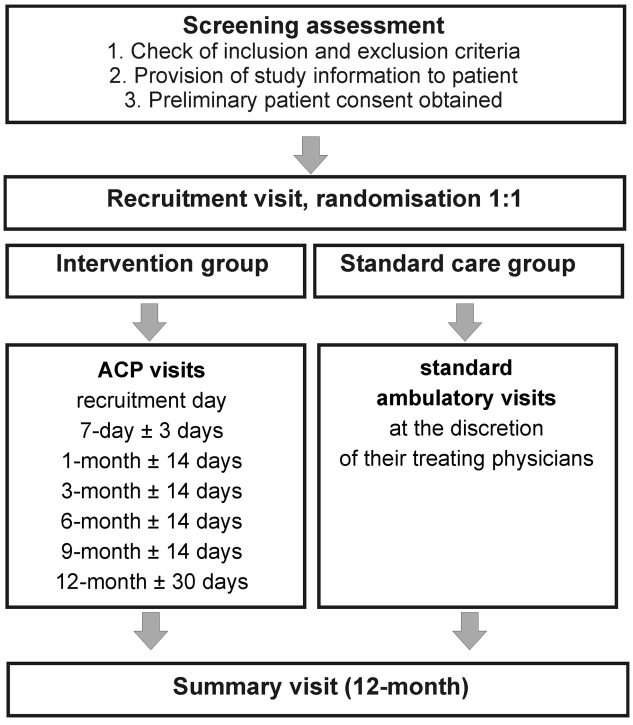
technique with random sequences of allowable block sizes of 4, 6, or 8. The randomization scheme was generated prior to the start of the trial and was blinded to the investigators. Subjects eligible for enrolment received consecutive randomization numbers and were allocated to a treatment group. Randomized subjects who terminate their participation in the study for any reason will retain their randomization number.

The AMULET study is conducted in ambulatory settings in 9 sites in Poland: 4 high-reference/university clinics (410 patients recruited), 2 district hospitals (83 patients recruited), and 3 outpatient specialist clinics (112 patients recruited).

Study procedures and schedule

The planned follow-up for each patient is 12 months (*Figure 1*). In the intervention group, 7 visits to the ACP are scheduled after the recruitment visit, and the final summary (follow-up) visit should be performed at 12 months ± 30 days after randomization. In the standard care group, the patients are advised during the recruitment visit to consult their physician or cardiologist in the standard healthcare system. After 12 months ± 30 days from randomization, standard care patients are also invited to a final

Figure 1 Trial flowchart. ACP, ambulatory care point.



follow-up visit. The treatment within the study period is at the discretion of their physicians.

The recruitment visit includes collecting current data about basic patient characteristics (i.e. constitution, medical history, physical examination, and socioeconomic status), comorbidities, and details of the most recent hospitalization for worsening HF (i.e. clinical state at admission and diagnostic tests). In both groups, patients are educated about a healthy lifestyle and the general principles of self-assessment. The follow-up visit will include a medical history update, recording of the patient's current clinical state, and reporting of endpoints. If a patient is unable to attend the follow-up visit, their data will be collected by telephone. At both the recruitment and final follow-up visits, patients will be asked to complete health-related quality of life questionnaires. The procedures performed at each visit are presented in *Table 2*.

Intervention

In the intervention group, the ACP visits are scheduled as per *Figure 1*. The planned timing of visits may be modified in extenuating circumstances, such as in patients who experience clinical deterioration, significant visit-to-visit changes in measured parameters, or interim hospitalizations for worsening HF. The comprehensive clinical assessment of patients in the ACP includes (1) assessment of symptoms and signs, (2) self-assessment of health condition and quality of life, (3) haemodynamic assessment, and (4) summary and recommendations.

The mandatory physical examination and reporting of symptoms are performed by the nurse at every ACP visit and include information on intensity of symptoms according to the NYHA classification system, breathlessness, orthopnoea, nocturnal cough, wheezing, loss of appetite, palpitations, syncope, weight gain (>2 kg/week), peripheral oedema, ascites, and tachypnoea. The physician examines patients only at the first two ACP visits. The self-assessment of health condition and quality of life at each visit is based on the European Quality of Life 5D Questionnaire (EQ-5D) questionnaire and a 10-point visual analogue scale (VAS; 0 being the poorest state of health and 10 being the best). Data regarding inter-visit modifications in pharmacotherapy and cardiac events are also collected.

The ACP nurses were recruited based on their experience in caring for HF patients. At all study sites, ACP nurses and supervising cardiologists were given training sessions on performing study procedures and using the telemedicine web service before starting the study. All sites were also equipped with written training instructions and presentations. Medical and technological consultants were available for support by telephone from Monday to Friday, 7 a.m. to 7 p.m. At three of the sites, the medical staff had previously gained practical experience in bioimpedance

Table 2 Study procedure and flow

		Ambulatory visits (intervention group only)				
	Screening	Recruitment visit	Recruitment day	7 days	1, 3, 6, 9 and 12 months	Follow-up visit
Verification of inclusion and exclusion criteria	x					
Provision of study information to patient	x					
Preliminary patient consent obtained	x					
Written patient consent obtained		x				
Randomization		x				
Medical history (including the most recent echocardiogram)		x				x
Physical examination and reporting of signs and symptoms (performed by a nurse)			x	x	x	
Physical examination and reporting of signs and symptoms (performed by a physician)		x	x	x		x
Recording of current medication use		x	x	x	x	x
Health questionnaires (SF-36, MLwHF, and EHFScBS)		x				x
Self-assessment of health condition (EQ-5D and VAS)			x	x	x	
Impedance cardiography			x	x	x	
Body composition (impedance scale)			x	x	x	
Education		x	x	x	x	x
Physician teleconsultation with remote therapeutic decision-making based on the recommendation support module					x	
Recording of endpoints data			x	x	x	x

EHFScBS, European Heart Failure Self-care Behaviour Scale; EQ-5D, European Quality of Life 5D Questionnaire; MLwHF, Minnesota Living with Heart Failure Questionnaire, SF-36, Short Form Survey; VAS, 10-point visual analogue scale.

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methods by participating in the aforementioned pilot study.[30]

The ACP nurse performs ICG (Cardioscreen 2000, Medis, Illmenau, Germany) and assessment of body composition (MC-418MA Composition Analyzer, Tanita, Tokyo, Japan). The collected data are entered into the telemedicine web service in real time and include automated transfer of measured parameters from the aforementioned diagnostic devices. The following vital signs were selected as the treatment targets: heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), thoracic fluid content (TFC) and its visit-to-visit change (ΔTFC), visit-to-visit change in body mass (ΔBM) and visit-to-visit change in total body water (ΔTBW). The complete data set is accessible online to the supervising cardiologist who will be contacted by text message or e-mail when the clinical and haemodynamic assessments are completed. The cardiologist's decision-making is based on a recommendation support module (RSM), which presents predefined target values and alarms (*Figure 2*, *Table 3*). For example, if TFC value falls within the range of green right-side alarm, the recommendation will be '*consider increased dose of diuretic*'. The default alarm ranges of RSM were developed basing on current guidelines,[1] that define optimal SBP, DBP, HR and permissible BM fluctuations, and our previous experience on TFC assessment.[29]

The supervising physician cross-references RSM indications with the patient's clinical data (nurse assessment and patient self-assessment) and gives final recommendations. In case of discrepancies, the physician's decision always supersedes the RSM indication. At the end of the visit, the patient remotely receives feedback and advice concerning his or her health condition, therapy recommendations, and the date of the subsequent visit. The physician also redefines individualized RSM optimal target values for the next visit, if needed.

Study outcomes

Data on all outcome measures are collected prospectively while consecutive visits. To avoid loss of data, the phone contact with patient and/or his or her relative is also allowed. An Endpoint Adjudication Committee (EDA) (listed in Appendix B), which is blinded to the treatment assignment of the patients, is appointed to take responsibility for determining whether the endpoint criteria (Appendix A) are met for the reported events.

The primary composite endpoint is defined as cardiovascular death or unplanned HF hospitalization during the 12 months of follow-up, whichever occurs first. The other study endpoints are listed in *Table 4*.

Statistical considerations

Sample size calculation

It was estimated that after controlling the family-wise type I error rate at a two-sided α level of 0.05, an enrolment of 296 subjects per treatment group would provide 80% power to detect a hazard ratio of 0.626, which corresponds to the assumption that the occurrence of events representing the combined primary endpoint (cardiovascular death and unplanned HF hospitalizations) would be 30% in the standard care group and 20% in the intervention group. The proportion of events in the standard care group corresponds to the data from the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT), which states that the combined endpoint of mortality or HF hospitalization within 1 year occurred in 36% of patients discharged after hospitalization due to acute HF.[35] It also corresponds to the observations in the Polish subpopulation (~30%) of the Hospital in Heart failure (HHH) study.[36] The assumed HR for the primary endpoint falls within the range of 0.53 to 0.80 reported for telemedicine interventions by Kotb *et al*.[37]

Analysed datasets

An independent Data Monitoring Committee (DMC) (Appendix B) has been appointed to oversee the data gathering process. The full analysis set will consist of subjects who were randomized to treatment according to the *intention-to-treat* principle. A secondary *per-protocol analysis* will also be performed.

Analysis methods

Baseline measurements and demographic characteristics will be summarized for patients in each treatment arm. Descriptive statistics will include means and standard deviations (or medians and interquartile ranges in cases of deviation from the normal distribution) for continuous variables as well as frequencies and percentages for categorical variables. The differences in baseline features between the groups will be tested using the independent Student's *t*-test (or Mann–Whitney *U* test in cases of violation of the normality assumption) for continuous variables and the Pearson χ^2 test (or the Fisher's exact test in cases of less than five expected frequencies in each cell of a contingency table) for categorical variables. The associations between two variables will be assessed using the Pearson, Spearman, or Cramer V correlation coefficients, where appropriate**.**

The Kaplan–Meier method will be used to estimate survival curves for *time-to-event* endpoints, including the primary composite endpoint. The log-rank test will be used to assess between-group differences in survival probabilities and the Cox-proportional hazard regression with Efron's method of handling ties will be used to define HRs and the corresponding 95% confidence intervals for the magnitude

of the treatment difference. The generalized estimating equations and generalized linear random-effects models will be used for longitudinal data. The percentage of days lost due to all-cause mortality or unplanned HF hospitalizations will be calculated by dividing the number of days lost due to death or unplanned HF hospitalizations by the intended duration of follow-up. For patients who die, the number of days lost between the date of death and the date of intended follow-up plus the number of days spent in hospital for unplanned HF hospitalizations will be counted. For patients who complete the study as planned or who withdraw prematurely from follow-up, the fraction of days lost is defined as the number of days lost divided by the follow-up time achieved (i.e. up to the cut-off date).

Prespecified subgroup analyses accompanied by interaction tests will be performed for the primary outcome to assess the consistency of AMULET intervention effects across the following factors:

1 gender: males versus females;
2 estimated glomerular filtration rate (eGFR) $<$ 60 mL/min versus stage 2 or lower (eGFR $\geq$60 mL/min);
3 LVEF (%): $<$ 40% versus 40–49%;
4 aetiology of HF: ischaemic versus non-ischaemic;
5 age: $\geq$65 years versus $<$65 years;
6 time between enrolment into the study and discharge: early ($\leq$30 days) versus late ($>$30 days); and
7 high-reference/university clinics versus district hospitals/outpatient specialist clinics.

P-values of less than 0.05 (two-sided) will indicate statistical significance for all tests.

Discussion

Symptoms and clinical signs occur fairly late in the course of decompensated HF and are not useful indicators for preventing hospitalization. About half of all patients with HF will be readmitted to hospital within 6 months of discharge, as they are at risk of not only HF progression but also functional decline, iatrogenic injuries and infections.[1,10] Thus, there is a substantial need for innovative delivery care models that can provide higher level of outpatient care.[1,38]

Figure 2 The example of recommendation support module (RSM) presentation. SBP, systolic blood pressure, DBP, diastolic blood pressure, HR, heart rate, TBW, total body water, TFC, thoracic fluid content.

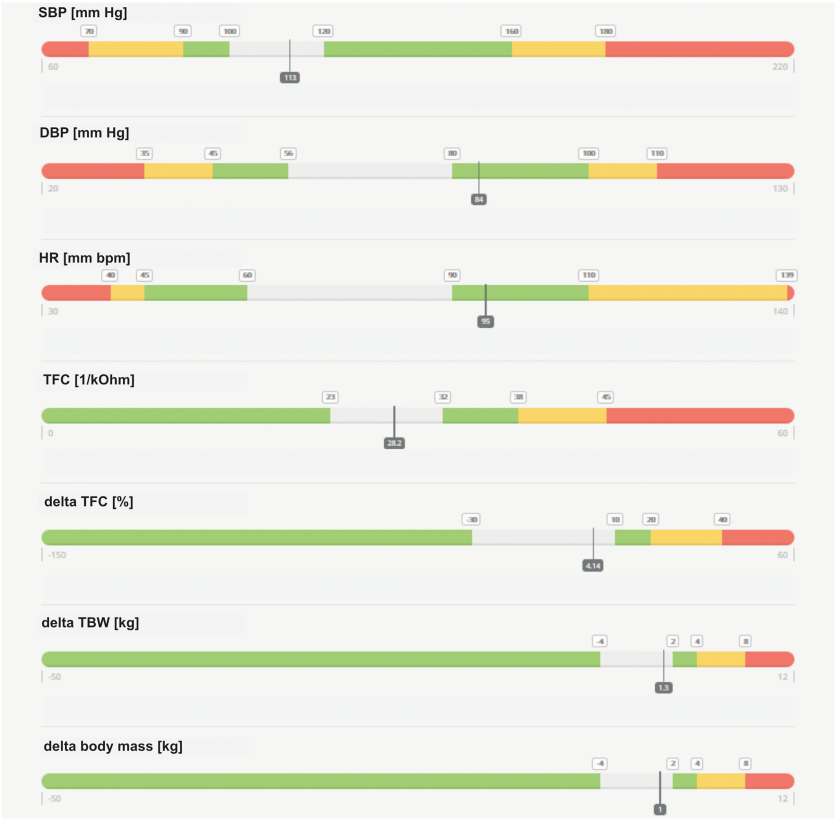

Table 3 Alarm grading and recommendations

Alarm grading	Recommendations
White	'*Maintain treatment*': no changes in drug dosage are recommended and direct physician consultation is not needed.
Green	'*Consider treatment modification*' *and/or* '*consider bringing forward the next visit*': there are slight deviations in the patient's haemodynamic parameters. Eventual treatment modification could be required via teleconsultation but an in-person examination by a physician is not needed. This also suggests that changes in drug dosage (either an increase or decrease) and/or discontinuation or addition of drugs may be necessary.
Yellow*	'*Modify treatment*' *and* '*recommend in-person physician consultation within 72 h*': there are significant deviations in the patient's haemodynamic parameters. As such, treatment modification could be prescribed via teleconsultations, but an in-person examination by a physician is necessary within 72 h to (1) verify the patient's clinical state and (2) evaluate the effect of recommended changes in the therapy.
Red*	'*Urgent in-person physician consultation recommended within 2 h*': there are critical deviations in the patient's haemodynamic parameters, and the patient is endangered and cannot leave the ACP without an in-person examination by a physician. If the physician is available, she/he should attend to the patient within 2 h. Otherwise, the patient should be referred to an emergency department.

*The ACP nurse conducting the visit will also be able to trigger the Yellow and Red alarms based on her own overall assessment of the patient, independently of RSM indications.

Table 4 Study endpoints

Primary composite endpoint
- Cardiovascular death* and/or unplanned HF hospitalization* during the 12 months ± 30 days of follow-up

Secondary endpoints (during the 12 months ± 30 days of follow-up)
- Cardiovascular death*
- Death due to worsening HF*
- Death for any cause
- Unplanned HF hospitalization*
- Unplanned cardiovascular hospitalization*
- Unplanned hospitalization* for any cause
- Number of unplanned HF hospitalization(s)*
- Days lost due to unplanned HF hospitalization(s) or all-cause mortality*

Surrogate endpoints
- Change in health-related quality of life indicators (SF-36/Minnesota Questionnaire score) between baseline and after 12 months (±30 days) of follow-up
- Change in NYHA functional class between baseline and after 12 months (±30 days) of follow-up
- Achieved daily doses (% of guideline-required target dose) of the following medications: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists and angiotensin receptor-neprilysin inhibitors after 12 months (±30 days) of follow-up
- Final doses of diuretics (furosemide, torasemide, hydrochlorotiazide, and indapamide) after 12 months (±30 days) of follow-up

*Adjudicated by the Endpoint Adjudication Committee (EAC).

Most telemedicine clinical trials in HF have focused on home telemonitoring. Their results are inconsistent and incomparable because of the heterogeneity in the study groups, implemented devices and telemedicine systems. Most randomized prospective trials published since 2000 have revealed some advantages of telemonitoring, but only a few have demonstrated its superiority to controls for the primary endpoints.[11–18] The Tele-HF (Telemonitoring to Improve Heart Failure Outcomes) and WISH (Weight monitoring in patients with severe heart failure) studies were neutral for nurse-supervised teletransmission of body mass and clinical symptoms.[14,15] In the BEAT-HF (Better Effectiveness After Transition—Heart Failure) study, 180 days of teleintervention based on remote patient monitoring (blood pressure, heart rate, body mass, and symptoms) failed to reduce all-cause hospital readmission when compared with standard care.[17] However, in a secondary analysis, Haynes *et al*.[39] showed that every day of good patient adherence resulted in a 19% decrease in mortality and an 11% decrease in the rate of hospitalization in the following week.

Additionally, the TIM-HF (Telemedical Interventional Monitoring in Heart Failure) trial, which was based on complex in-home telemonitoring of vital signs (referred to as remote patient management [RPM]), had no effect on mortality (all-cause and cardiovascular) and HF hospitalizations.[18] However, its second edition, TIM-HF2 (Telemedical Interventional Monitoring in Heart Failure II), which was performed in a modified manner with a better-defined HF population and redefined endpoints, revealed that RPM was beneficial in reducing the percentage of days lost to unplanned cardiovascular hospitalizations (4.9% vs. 6.6%, HR = 0.80; P = 0.046) and all-cause mortality (HR = 0.70; P = 0.028).[12] The value of these results was so significant that the expert consensus report of the Heart Failure Association of the European Society of Cardiology indicated home monitoring similar to the one used in TIM-HF2 as worthy of

consideration for patients with HF.[40] The *post hoc* analysis of the TIM-HF2 trial emphasized the importance of patient selection. HF patients with atrial fibrillation (AF) were revealed to be a more promising target population than those with sinus rhythm; the AF subjects receiving teleintervention had more days alive out of hospital (5.6 vs. 9.4%, $P = 0.015$) and lower mortality (9.2% vs. 14.5%; $P = 0.050$) in comparison with the controls. These effects were less prominent in the sinus rhythm group ($P = 0.45$ and $P = 0.16$, respectively).[41]

The discussion on telemonitoring will certainly continue. This is in view of the recently published results of OSICAT (Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Tele-cardiology) trial,[42] in which remote intervention was again ineffective for the primary endpoints (all-cause mortality and unplanned HF hospitalizations). Only several populations benefited from telemonitoring: patients in NYHA class III/IV (HR = 0.71; $P = 0.02$), socially isolated subjects (HR = 0.62; $P = 0.043$), and those strictly adherent to body mass measurement (HR = 0.63; $P = 0.006$).

Our concept is not intended to compete with home monitoring trials but to fill a niche for telemedicine solutions in stationary ambulatory care. We offer a new pathway for HF patients by responding to the shortage of cardiologists in the outpatient healthcare system. The development of the proposed network model of ACP would enable a larger group of patients to benefit from modern technologies and teleconsultations with specialists. The potential advantages of this concept include (1) individualized approach and early detection of cardiovascular deterioration, (2) early therapeutic intervention, (3) optimization of pharmacotherapy in accordance with guidelines, (4) continuous, uninterrupted care from hospital admission to outpatient treatment, and (5) improved availability of consultations with specialists. A multifunctional telemedicine web service will be developed with the hope of broadening its application in routine clinical practice.

We are aware that the proposed concept is burdened by its limited ability to detect decompensation between planned consultations. Therefore, in the future, we intend to further enrich the final AMULET healthcare model with home monitoring devices targeted at patients who are at the highest risk of HF deterioration.

This proposed care system can contribute to the resolution of significant challenges in the current healthcare system. The optimization of the treatment of HF patients and the consequent improvement of their prognosis may yield relevant clinical, social, and economic benefits.

The AMULET trial is an important randomized controlled trial that will assess for the first time whether comprehensive interventions based on individualized haemodynamic assessment and teleconsultations can reduce mortality and the rate of readmissions in HF patients. The results of the AMULET study should provide further clarification of the benefits of telemedicine in patients with HF.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Author contributions

Paweł Krzesiński did the conception and design of the research, obtaining funding and supervising the work, drafting manuscript, critical revision of the manuscript for important intellectual content; Janusz Siebert did the conception and design of the research, obtaining funding and supervising the work, drafting manuscript, critical revision of the manuscript for important intellectual content; Ewa Anita Jankowska carried out the conception and design of the research, obtaining funding and supervising the work, drafting manuscript, critical revision of the manuscript for important intellectual content; Waldemar Banasiak did the conception and design of the research, critical revision of the manuscript for important intellectual content; Katarzyna Piotrowicz did the conception and design of the research, acquisition of data, critical revision of the manuscript for important intellectual content; Adam Stańczyk carried out the conception and design of the research, acquisition of data, critical revision of the manuscript for important intellectual content; Agata Galas did the conception and design of the research, acquisition of data, critical revision of the manuscript for important intellectual content; Andrzej Walczak did the conception and design of the research, critical revision of the manuscript for important intellectual content; Piotr Murawski did the conception and design of the research, critical revision of the manuscript for important intellectual content; Paweł Chrom did the conception and design of the research, drafting manuscript, critical revision of the manuscript for important intellectual content, statistical analysis plan; Piotr Gutknecht did the conception and design of the research, acquisition

of data, critical revision of the manuscript for important intellectual content; Paweł Siwołowski did the conception and design of the research, acquisition of data, critical revision of the manuscript for important intellectual content; Piotr Ponikowski did the conception and design of the research, critical revision of the manuscript for important intellectual content; Grzegorz Gielerak did the conception and design of the research, obtaining funding and supervising the work, drafting manuscript, critical revision of the manuscript for important intellectual content. We would like to thank the medical staff of our departments for the nursing care and data collection and administrative staff for the organizational preparation of the project.

Appendix A: Adjudication definitions for death/hospitalization events

Cardiovascular death: a death will be classified as cardiovascular if related to (but not limited to) the following: acute myocardial infarction, arrhythmia, heart failure, pulmonary embolism and cerebrovascular disease (e.g. stroke). Unless an unequivocal non-cardiovascular cause is established, a death will be considered as cardiovascular**.** Death will not be classified as cardiovascular if there is a clear non-cardiovascular reason for death (i.e. suicide, violence, accidents, non-cardiovascular infection, renal failure of non-cardiovascular origin, respiratory insufficiency of non-cardiovascular origin, cancer and other non-cardiovascular causes).

Death due to worsening of heart failure: a death will be classified as being due to heart failure if heart failure is considered a major cause/factor leading to death. Death resulting from mechanical dysfunction of the heart (even if the terminal event is likely an arrhythmia or sudden cardiac death) will be classified as death due to heart failure when preceded by persistent or frequently recurrent NYHA class IV symptoms, an escalating need for supportive therapy and, in many cases, evidence of organ failure (e.g. renal). Subjects with cardiogenic shock or pulmonary oedema resistant to therapy are included in this category.

Unplanned hospitalization: an unplanned hospital admission (the patient must not have signs or symptoms of worsening disease and must not be in need of intensified therapy at any time during the hospitalization) resulting in an overnight stay with date change of total duration more than 24 h (including emergency room visits). Hospitalizations for diagnostic procedures, elective interventions (such as device implantation) or rehabilitative measures are considered to be planned hospitalizations and will not be counted as unplanned hospitalization events.

Unplanned cardiovascular hospitalization: an unplanned hospitalization will be classified as cardiovascular if related to cardiovascular disease or development of a cardiovascular condition during a hospitalization that is considered to have caused a prolonged hospital stay (including heart failure, angina, myocardial infarction, syncope, arrhythmia, stroke, transient ischaemic attack, acute peripheral vascular emergencies, pulmonary embolism or other cardiovascular conditions). Unless an unequivocal non-cardiovascular cause is established, the reason for hospitalization will also be considered as 'cardiovascular'. If the patient develops heart failure during hospitalization (but heart failure is not the reason or a major component of the respective hospital admission), this will not be judged a 'hospitalization for or with worsening heart failure' but will be deemed a 'cardiovascular hospitalization' if the respective criteria are fulfilled.

Unplanned hospitalization for heart failure: an unplanned hospitalization will be classified as being for worsening of heart failure if an admission to hospital is necessitated by heart failure and is primarily for its treatment or when heart failure becomes a major component of the patient's hospital admission. A patient admitted for this reason should show signs and symptoms of worsening heart failure (at least two of the following: shortness of breath/dyspnoea on exertion/at rest, orthopnoea, (paroxysmal) nocturnal dyspnoea, pulmonary oedema/congestion [rales and/or radiological signs of congestion], increasing peripheral oedema, hepato-jugular reflux, elevated jugular venous pressure) and require treatment with IV diuretics, IV vasodilators and/or IV inotropes (excluding digoxin).

Every attempt will be made to obtain adequate data for classification.

Appendix B: List of the amulet committees and investigators

Lead Principal Investigator: Paweł Krzesiński (Military Institute of Medicine, Warsaw, Poland).

Trial Steering Committee (EC) (supervises the conduct of and assumes academic responsibility for the trial): Grzegorz Gielerak (Military Institute of Medicine, Warsaw, Poland); Piotr Ponikowski (Wroclaw Medical University, Wroclaw, Poland); Waldemar Banasiak (4th Military Hospital, Wroclaw, Poland); Ewa A. Jankowska (Wroclaw Medical University, Wroclaw, Poland); Janusz Siebert (Medical University, Gdansk, Poland); Andrzej Walczak (Military University of Technology, Warsaw, Poland).

Data Monitoring Committee (DMC) (oversees the safety of the patients and reviews the results of the interim analyses): Robert Ryczek (Military Institute of Medicine, Warsaw, Poland); Piotr Murawski (Military Institute of Medicine, Warsaw, Poland); Agnieszka Opłocka (Military Institute of Medicine, Warsaw, Poland); Agnieszka Jurek (Military

Institute of Medicine, Warsaw, Poland); Adam Kołodziej (Wroclaw Medical University, Wroclaw, Poland).

Endpoint Adjudication Committee (EAC) (assumes responsibility for classifying all deaths and for determining whether prespecified endpoint criteria are met for non-fatal events): Marek Kiliszek (Military Institute of Medicine, Warsaw, Poland); Krystian Krzyżanowski (Military Institute of Medicine, Warsaw, Poland); Beata Uziębło-Życzkowska (Military Institute of Medicine, Warsaw, Poland); Robert Zymliński (Wroclaw Medical University, Wroclaw, Poland); Łukasz Lewicki (Medical University, Gdansk, Poland).

Principal Investigators/Centre Leaders: Paweł Krzesiński, (Military Institute of Medicine, Warsaw, Poland); Paweł Siwołowski, (4th Military Hospital, Wroclaw, Poland); Piotr Gutknecht, (Medical University, Gdansk, Poland).

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