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Effectiveness of an interactive platform, and the ESC/HFA heartfailurematters.org website in patients with heart failure. Design of the multicenter randomised e-Vita heart failure trial

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Abstract

Aims: Electronic health support (e-health) may improve self-care of patients with heart failure (HF). We aim to assess whether an adjusted care pathway with replacement of routine consultations by e-health improves self-care as compared to usual care. In addition, we shall determine whether the ESC/HFA website heartfailurematters.org (HFM website) improves self-care when added to usual care. Finally, we aim to evaluate the cost-effectiveness of these interventions.

Methods: A three-arm parallel randomised trial will be conducted. Arm 1 consists of usual care; arm 2 consists of usual care plus the HFM website; and arm 3 is the adjusted care pathway with an interactive platform for disease management (e-Vita platform), with a link to the HFM website, which replaces routine consultations with HF nurses at the out-patient clinic. In total, 414 patients managed in ten Dutch HF out-patient clinics or in the general practices will be included and followed for 12 months. Participants are included if they have had an established diagnosis of HF for at least 3 months. The primary outcome is self-care as measured by the European Heart Failure Self-care Behaviour Scale (EHFScB scale). Secondary outcomes are quality of life, cardiovascular- and HF-related mortality, hospitalization, and its duration as captured by hospital and GP registries, use and user satisfaction of the HFM website, and cost-effectiveness.

Discussion: This study will provide important prospective data on the impact and cost-effectiveness of an interactive platform for disease management and the HFM website.

Trial registration: ClinicalTrials.gov NCT01755988

Keywords: Telemedicine, Heart Failure, Self-care, Mortality and Hospitalization
Introduction

Heart failure (HF) is a chronic progressive disease with an increasing prevalence with age (1), a major impact on health status, hospital admissions for HF exacerbations and on the health care budget (2). This problem is growing because of the ageing of the population and improved care following acute cardiac events (3) while health care budgets are cut. Educational programs focussed on patient self-care can result in a reduction in both HF-related and all-cause hospitalization rate (4). However, these programs demand considerable human resources, and are not cost saving (5). In the Netherlands, the majority of hospitals have HF out-patient clinics with HF nurses providing care. Because these programs are highly time- and money consuming it will become a challenge to manage the growing number of HF patients in the near future. Efficient incorporation of electronic health (e-health) replacing routine consultations (mainly face-to-face contacts at out-patient clinics) would reduce the time investment of health care workers and thus reduce health care costs. By regular monitoring of vital signs such as blood pressure, heart rate and weight, with a patient-tailored approach, imminent exacerbations could be identified early and unplanned hospitalizations prevented. With e-health, for example a website with information targeted at patients and their family/carers, such as the website heartfailrematters.org (HFM website) and an interactive platform for disease management (e-Vita platform), large numbers of individuals could be monitored and managed efficiently. Apart from preventing hospitalisations, such e-health tools may help improve health behaviours (6). Earlier studies assessing the effect of combining e-health tools focussing on disease management with (real time) telemonitoring facilities showed promising results in patients with chronic diseases such as HF, although neutral studies have been published (7, 8).
Moreover, these interventions have exclusively been evaluated ‘on top of’ usual care, and not as a replacement for routine face-to-face consultations with HF nurses at the out-patient clinic.

We aim to assess the effects of the HFM website and the e-Vita platform, with a link to the HFM website, which replaces routine consultations with HF nurses at the out-patient clinic in patients with HF.

Objectives

To assess whether the e-Vita platform improves self-care in patients with HF compared to usual care.

To assess whether the HFM website improves self-care in patients with HF compared to usual care.

To assess whether the e-Vita platform and the HFM website decrease secondary outcomes.

To evaluate how patients use and perceive the HFM website.

To determine the cost effectiveness of both interventions.
Methods

Study design: A three-arm parallel multicentre randomised trial. Arm 1 consists of usual care; arm 2 consists of usual care plus the HFM website; and arm 3 is the adjusted care pathway with the e-Vita platform, with a link to the HFM website, which replaces routine consultations with HF nurses at the out-patient clinic. Four hundred and fourteen patients with established diagnosis HF managed in 10 Dutch HF out-patient clinics or in the primary care practices in the vicinity of these will be randomly allocated to one of the three arms, and followed for one year.

Study population and recruitment

HF patients from the out-patient clinic will be asked to participate by HF nurses. For eligibility criteria see table 1.

Invitation to the study of patients known with HF in primary care will be done by a poster and reply-card at the GPs office. Eligibility criteria for HF patients primarily managed in general practices are identical to patients recruited from the out-patient clinics. For inclusion in the study, these patients will be referred to the nearest participating HF out-patient clinic to allow for baseline measurements and randomisation, and when necessary confirm the diagnosis of HF and providing additional and essential education. If the patient is allocated to arm 1 or 2 he is further managed by the GP. Patients allocated to arm 3, however, are further managed by the HF nurses at the out-patient clinic, since it was not feasible to have participating GPs get accustomed to and maintain the e-Vita platform for a single patient.

We anticipate that we will not be able to recruit many patients solely managed in primary care for several reasons. First, in order to participate these patients have to be instructed by health-care providers outside the primary care setting with whom they are not familiar. Secondly, these patients should be referred to the out-patient clinic to undergo additional investigations for
confirmation of the presence of HF. Both aspects are serious barriers for patients from primary care to participate in our trial.

Written informed consent will be obtained during the first study visit at the HF out-patient clinic before any study procedure is undertaken.

**Randomisation**

Eligible patients will be randomised individually by computerised block randomisation to one of the three arms. The maximum amount of participants per block will be nine.

**Study arms**

**Arm 1:** Allocated patients receive usual care from the cardiologist, HF nurse, and other health care workers at the HF out-patient clinic, and/or the GP and practice nurse in the primary care setting.

**Arm 2:** Allocated patients receive information about the HFM website from the HF nurse and will be instructed on how to use it. During the routine consultations with the HF nurse patients will be encouraged to use the website. Additionally, participants receive a leaflet with useful information about the website and every three months a reminder by e-mail.

**Arm 3:** Allocated patients follow an adjusted care pathway. They receive identical information on the use of the HFM website as participants in arm 2. In addition, the HF nurses will instruct the patients and their caretakers extensively on how to use the e-Vita platform for disease management. Patients will learn to record body weight, blood pressure and heart rate every day (or individually adjusted at a lower frequency by the HF nurse when stable) at a fixed time point. The vital parameters may vary during the day depending on, for example, fluid intake, timing of drug intake and exercise. By measuring these parameters at fixed time points, the measurements
of previous days can be used for comparison, and changes in the parameters will be least affected by fluctuations caused by other factors than change in health status. The results of these vital parameters are automatically forwarded to the e-Vita platform. Pre-specified alert limits are determined: for body weight (+1 kg in one day, +2 kg in three consecutive days, -3 kg in one day and +2 kg or -2kg from baseline body weight), systolic blood pressure (average of 140 mmHg (upper limit) and average of 90 mmHg (lower limit) for three consecutive days), diastolic blood pressure (average of 100 mmHg (upper limit) and average of 50 mmHg (lower limit) for three consecutive days) and heart rate (100 beats per minute (b.p.m.) (upper limit) and 50 b.p.m. (lower limit)). At the start, the limits are similar for all patients and cut-off points are based on the average HF patient on medication to keep him/her at an optimal blood pressure, heart rate and weight. However, to reduce the possibility of unnecessary alerts, we will encourage the HF nurses to adjust these limits for individual patients, in shared decision, with the patient, and when necessary after consultation of the GP.

If recordings of body weight, systolic blood pressure, and/or heart rate are outside the limits or if measurements are not recorded, the HF nurse will be alerted via the e-Vita platform. When necessary, the HF nurse will contact the patient by phone to ask for symptoms, and possibly adjust the disease management and/or medical treatment. She may also decide to let the patient visit the out-patient clinic, ask the GP to make a home visit, or let the patient present himself at the general practice or hospital.

In the Netherlands, all community-dwelling persons are enlisted with a GP, who is the ‘medical file holder’ of all these patients, including those managed in secondary care. GPs receive and archive letters and reports of all hospital specialists. Consequently, the GP is optimally informed about (changes in) patient’s comorbidities and medication, also in those with HF managed at the out-patient clinics. Therefore involvement of the GP in this intervention arm is crucial (9, 10). On
the e-Vita platform, comorbidities and medication will be kept up to date by the patient as are the reasons for changing or stopping or starting drugs. The nurse encourages the patients to do so, and the patients will be reminded by e-mail monthly. This can enhance self-management and patient empowerment. When the nurse has doubts about the ability of the patient to update comorbidities and medication on the platform, the local pharmacy will be called to check for changes in medication and the GP will be called to check for changes in comorbidities regularly. Finally, face-to-face consultations with the HF nurse will be on demand, or when considered necessary, but not on a routine basis.

At the start of the study, the HF nurses received a training of five hours on the study procedures and adjustment of the vital parameters within the e-Vita platform. In addition the study team and the helpdesk of the e-Vita platform were available to provide help by phone and e-mail during office hours.

**Usual care**

The participating Dutch HF outpatient clinics all provide similar ‘usual care’ that is based on the ESC guidelines (10). This care contains structured follow-up after hospitalisations by the cardiologist and HF nurse, with further up-titration of the HF medication, optimising adherence, HF education and personalised life style advice by the HF nurse. The structured follow-up consists of one to four face-to-face consultations per year; one with the cardiologist, and one to three with the HF nurse, and additional telephone consultations when necessary. The exact amount of face-to-face contacts, however, may somewhat differ per patient and per region.

**Study procedures (see figure 1)**
General characteristics at baseline will be obtained from all participants, including medical history, medication use, body weight, blood pressure, and heart rate.

Self-care, quality of life (QoL), HF knowledge and the evaluation of care will be assessed by questionnaires sent by e-mail at baseline, and after 3, 6 and 12 months. It will take approximately 60 minutes to complete those. For participants in arm 2 and 3, the use and the user satisfaction of the website will be assessed at baseline, and after 3, 6 and 12 months. Participants in arm 1 are asked to fill out these latter questionnaires only at the end of the study. Although the HF nurse will not encourage the use of the HFM website to patients in arm 1, they have free access to the website via the internet. By asking participants in arm 1 about the website only at the end of the study, ‘priming’ of searching for and using the website is reduced and loss of contrast between arm 1 and 2 is kept to a minimum.

Furthermore, blood tests will be done at baseline, and after 6 and 12 months.
Outcomes and measurements

In studies evaluating the effect of self-management tools in HF patients, the primary endpoint most often was mortality and/or hospitalisation (7, 9). We assume that education and skills-training with e-health tools will primarily enhance self-care (11) and thus will improve quality of life and probably reduce health care costs. Therefore we chose self-care as the primary outcome (see table 2).

Self-care is defined, as the decision and strategies undertaken by the individual in order to maintain life, healthy functioning and well-being(12). Self-care relies on personal resources and enables the person suffering from HF to be in charge of his own care. Self-care includes adherence to medication, diet, exercise, and daily weighing, but it also refers to behaviours such as seeking assistance in case of (progression of) symptoms (12). There are two validated instruments to measure self-care in HF; the European Self-care Behavioral scale (EHFScBs) and the Self-care of Heart Failure Index (SCHFI) (13). We chose to use the EHFScB scale, because it seems most appropriate for our Dutch study population as it has been validated in a Dutch population. With the EHFScB scale it is possible to quantify the behaviour that patients with HF undertake to maintain life, healthy functioning, and well-being. This scale includes self-reported consulting behaviours and adherence to regimen (daily weighing, adequate medication use, fluid intake, diet and exercise). The EHFScB scale contains nine items each with a 5 point Likert scale. The score can range from 9 to 45 points. A total score of 9 indicates optimal self-care and a score of 45 the most insufficient self-care (14). A recent telemonitoring study reported a statistically significant change of 2.0 points (15). Unfortunately, there is not yet consensus on which change in this score can be considered clinically meaningful. However, it is an important patient-reported outcome in HF (16), and as such assessing the clinical meaningful change is an important aspect, apart from the validity, reliability and responsiveness of this scale (17, 18). Our study can provide
important information to help define, together with other studies, which changes of the EHFScB scale may be considered as clinically meaningful.

Secondary outcomes are (1) health-related QoL generically measured with the short-form health survey with 36 questions (SF36) (19) and EuroQol five Dimensions (EQ-5D) (20), and disease-specific with the Minnesota living with HF questionnaire (MLHFQ) (21) (2) the use of the website and its user satisfaction measured by the ‘use of website’ and the website user satisfaction (WUS) (22) questionnaire, (3) disease-specific knowledge measured with the Dutch Heart Failure knowledge scale (DHFk) (23) and ‘questions on heart failure (QoHF)’ questionnaire,(4) patient satisfaction about their HF and the HF care in the three arms measured with a Visual Analogue Scale (VAS); this also enables us to assess how the patient experiences the replacement of face-to-face contacts with the HF nurse by e-health in the adjusted care pathway, (5) N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, renal function (estimated Glomerular Filtration Rate (eGFR)), and (6) cardiovascular-related mortality, HF-related mortality, cardiovascular-related hospitalizations, HF-related hospitalizations and number of days of HF-related hospitalisations as captured by hospital and GP registries. Disease specific mortality will be assessed by an independent committee of a GP and a cardiologist who are blinded to the study arm. The results of these secondary outcomes will be interpreted in an exploratory way and considered as hypothesis generating due to the relative small sample size of the study that is not specifically powered for these secondary outcomes. Finally, to calculate the cost-effectiveness of the interventions, all health care use (e.g. (telephone) consultations, medication, all-cause mortality, hospitalizations, visits to the GP and hospital) will be recorded and retrieved from the GP and hospital registries.
**Sample size**

The sample size calculation is based on an alpha of 0.05 and a power of 80% with ANOVA to detect a difference of 0.5 to 2.0 in self-care behaviour measured with the EHFScB scale. The estimated mean (SD) EHFScB scale score is 20 (5.54), based on unpublished data from a previous study (24).

The sample size calculation is based on a single comparison of the three study arms with an expected mean difference of the EHFScB scale score between arm two (usual care plus HFM website) and arm one (usual care), and between arm three (adjusted care pathway) and usual care of 0.5 and 2.0 points, respectively. These differences are based on previous studies (15, 25, 26).

Our loss to follow up rate is expected to be very low and we will impute missing outcome data based on state-of-the-art imputation techniques and by applying sensitivity analysis (27).

Based on these assumptions, the number of subjects in each study arm is 138 participants, which means we require 414 patients for the total study. This is around 46 subjects per out-patient clinic (including patients recruited from the general practices) resulting in approximately 16 patients per arm per clinic.

**Data analysis**

We will perform an intention to treat analysis. Primarily, the effects from the 12 months follow up will be determined, but also the effects at 3 and 6 months will be reported. Missing values will be imputed by multiple imputation methods (27).

The results on self-care will be compared between the three arms, using a one-way (to test for differences among two or more independent groups) analysis of variance test (ANOVA).

Secondary outcomes will be compared between the three arms, using the chi-square test for the dichotomous and categorical variables, and ANOVA for the continuous dependent variables.
The independent effect of the two interventions on the primary outcome (self-care) compared to usual care will be assessed by a multiple linear or logistic regression analysis. These techniques will also be applied to the secondary outcomes. Mortality and hospitalizations are analysed by a Cox-regression model to take into account time preceding death, with censoring for participation time.

Furthermore we will assess whether there is evidence of a difference in the effects of the two interventions in pre-specified subgroups according to age (<65, 65-74, 75-84, >85) and HF severity (based on NYHA functional class), by performing subgroup analyses and using interaction terms. Since the power of the trial is limited, these subgroup analyses will be exploratory in nature.

The study will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement (28) and ICH Guidelines for Good Clinical Practice.

**Economic evaluation**

In the economic evaluation, the balance between the costs and the health effects of the two interventions compared to usual care will be assessed.

We will include the direct health care costs (e.g. from hospitalisations, visits to the GP, medication use). Indirect costs outside healthcare will not be included as most patients will be retired which makes it difficult to make a reliable estimate of these.

For each patient, the total number of quality adjusted life years (QALYs) in the study will be calculated. The cost and effects QALYs will be integrated in cost utility analyses, with costs per QALY as the outcome. Incremental cost effectiveness ratios (ICERs) will be calculated by dividing the total costs in the arms by the effects (29). These ICERs will be presented in relation
to varying cost effectiveness thresholds (i.e. the amount society is willing to pay for an additional QALY).

**Regulation statement**

The study is conducted according to the principles stated in the current Declaration of Helsinki (30) and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO).

**Ethics committee approval**

The study has been approved by the medical ethical committee (METC) of the University Medical Center Utrecht (UMCU), the Netherlands.
**Discussion**

This study will provide important prospective data on the impact of the HFM website, and of an adjusted care pathway with the e-Vita platform, with a link to the HFM website, which replaces routine consultations with HF nurses on health outcomes of patients with HF. In addition, cost effectiveness of these interventions will be evaluated.

To our knowledge this will be the first study evaluating the HFM website. Active involvement of GPs and critically taking care of comorbidities and all drugs with potential interactions, plus the emphasis on patient-centred and shared decision making are unique aspects of this study. In addition, the e-Vita platform will not be evaluated on top of usual care (7) but as a replacement of face-to-face scheduled routine visits to HF nurses. Importantly, the e-Vita platform allows the HF nurse to tailor treatment advices based on both vital signs (weight, blood pressure, and heart rate) and up-to-date information on drug use and comorbidities. The frequency of measurement of vital signs will be patient-centred after shared decision making, being more lenient in those stable and well-equipped and more stringent in those with a high tendency to exacerbations. These adaptations prevent ‘fatigue of alerts’ in both nurse and patient, targeting the care at those who need it most. In addition the nurse can adjust the pre-specified limits of the vital parameters in the e-Vita platform to the patient’s individual situation, this also prevent unnecessary alerts and phone calls to the patient. Such tailored monitoring and treatment potentially enhances compliance of the patient (15).

The fact that our study was performed in a Dutch HF population may lead to an underestimation of the effect of the interventions in other countries because the care for HF is rather well organised in the Netherlands, as shown in large HF management program studies (31, 32).

In addition we use, a so called, pragmatic trial design. Extraneous effect (effects outside of the effect of interest for example changes in behaviour) are accepted as being inherently part of the
intervention strategy and blinding of patients and health care professionals is not indicated. The strength of such a design is that the intervention as a whole is evaluated. However, a potential pitfall may be that because the health care professionals are aware of the allocation of the patient, they could influence health care use (e.g. face-to-face contacts, hospitalizations) related to a specific study arm. We, however, expect this potential bias to be limited because the health care professionals are not involved in development of the platform and do not receive any financial incentive to take part in the study.

**List of abbreviations**

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<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>e-health</td>
<td>electronic health</td>
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<td>HFM website</td>
<td><a href="http://www.heartfailurematters.org">www.heartfailurematters.org</a></td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
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<td>GP</td>
<td>general practitioner</td>
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<tr>
<td>e-Vita platform</td>
<td>interactive platform for disease management, with a link to the HFM website</td>
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<td>EHFScB scale</td>
<td>European Heart Failure Self-care Behaviour scale</td>
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<td>MLHFQ</td>
<td>Minnesota Living with Heart Failure Questionnaire</td>
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<td>NYHA</td>
<td>New York Heart Association functional class</td>
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<tr>
<td>QALYs</td>
<td>quality adjusted life years</td>
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<td>ICERs</td>
<td>incremental cost effectiveness ratios</td>
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Authors’ contribution
FR and AH conceived the study idea and raised funding. All authors participated (KW, BB, KD, TJ, AH and FR) in the design of the study and the complete study protocol. KP, BB, AH and FR will manage the study and data collection. KP wrote the first draft and all other authors (BB, KD, TJ, AH and FR) edited previous versions of the manuscript. All authors critically reviewed and approved the final draft of the manuscript. FR is guarantor of the study.

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Conflicts of interest
None declared.
References


Table 1 Inclusion and exclusion criteria

**Inclusion criteria**
Diagnosed with HF* (independent of ejection fraction) for at least three months to allow for sufficient time for the essential education and up titration of drugs. The diagnosis of HF needs to be established according to the guidelines of the ESC¶ (suggestive symptoms and structural or functional abnormalities compatible with ventricular dysfunction on echocardiography in rest).
Sufficient cognitive and physical function i.e. able to fill out the questionnaires and perform blood pressure measurements and weighing (by standing on a weighing scale).
Aged 18 years or over.

**Exclusion criteria**
Non-availability of internet and e-mail.
Inability of the patient or his/her family to work with internet and e-mail.
Inability of the patient or his/her family or care takers to read and understand Dutch.

*HF=heart failure, ¶ESC=European Society of Cardiology*