E-health in heart failure

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E-health bij hartfalen
(met een samenvatting in het Nederlands)

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Voor mijn opa's

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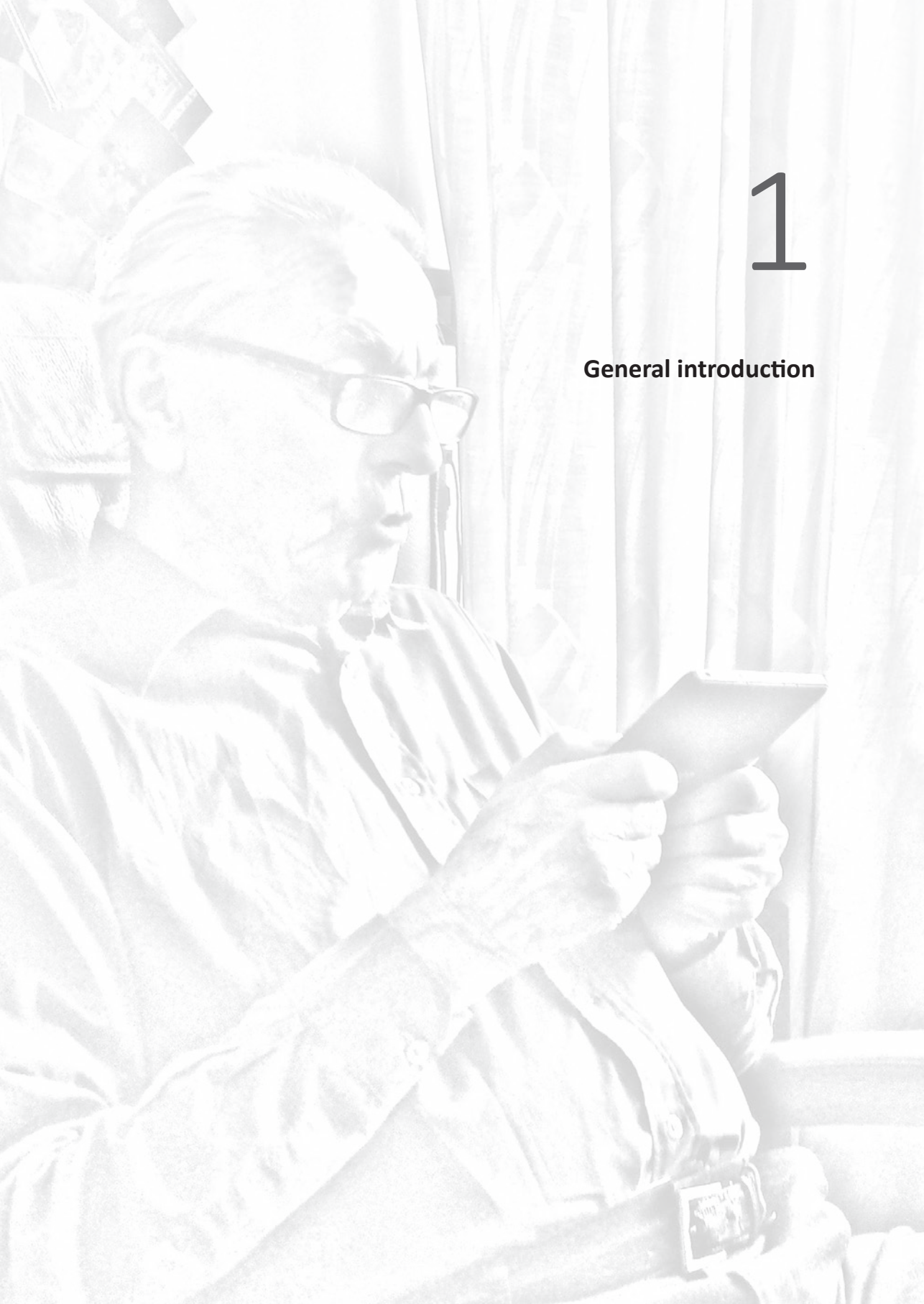

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General introduction

The case of Mr. Weeda

Mr. Weeda is 69 years old. Two years ago he rather abruptly developed shortness of breath that escalated within days in severe breathlessness resulting in a hospitalisation for some days. In hospital heart failure (HF) was diagnosed. He is known with diabetes for 10 years and has serious problems in moving around due to osteoarthritis of both knees. He lives on his own after his wife passed away six years ago. He has three children living around a two to three hours' drive away. The neighbours look after Mr Weeda. They help him with buying groceries and removing garbage. The routine consultations at the outpatient clinic with the HF nurse are troublesome because he has no car, and finds it difficult to travel by public transport. Because of the busy schedules of his neighbours and children, they can only occasionally accompany him. Moreover, after a visit to the outpatient clinic his knees always hurt more for a few days.

It would be great if the travelling to the outpatient clinic could be skipped, without jeopardizing the way his HF is monitored or losing the personalised HF advices from his beloved HF nurse. Can e-health help?

Heart failure

HF is a chronic progressive syndrome characterized by the heart's inability to pump enough blood to meet the body's requirements. Common symptoms are breathlessness, ankle swelling, and fatigue. (1) The estimated prevalence is 23 million worldwide, (2) and increases with age. (3) The prevalence is expected to rise even further because of aging of the population and improved survival after acute cardiac events. (4)

HF has a major impact on the health status of patients, often leads to unplanned hospitalisations, and has a high impact on the total healthcare budget (i.e. 1 to 2%). (5, 6) For patients with HF multiple evidence-based treatments are available, notably drug and device therapy, but also multifaceted multidisciplinary management programs targeting self-care, including lifestyle advices, adherence to therapy, monitoring of vital functions, and with education on HF. (7)

In several countries, such HF disease management programs are nowadays typically organised by HF outpatient clinics with cardiologists and HF nurses in the lead. (1) Although effective, such programs are expensive and labour-intensive: relatively few patients per healthcare worker can be served. Given the budgetary constraints on healthcare expenditure, especially in view of the increasing number of older adults with multiple morbidity, in nearly all western countries, there is a need for more lean, less costly types of HF management that remains capable of serving the increasing number of patients. One such a strategy would be to replace routine contacts with HF nurses by e-health in stable HF patients who are sufficiently educated on HF and self-care management. (8) As an additional benefit, the autonomy and the self-care of the patient may increase, and along with that possibly a reduction in the need of (unplanned) hospital care and thus even eventually all-cause mortality.

E-health

'E-health is defined as an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve healthcare locally, regionally, and worldwide by using information and communication technology.' (9) Telemonitoring (i.e. remote monitoring of vital signs and symptoms in people with acute or chronic conditions) is an example of an e-health tool and falls under the broad term 'e-health'. Importantly, however, in this thesis telemonitoring is a component of one of the evaluated e-health tools. Some previous studies assessed the effect of e-health tools (e.g. telemonitoring) focussed on HF disease management and showed promising effects on hospitalisations and survival. (10) Others, however, reported neutral results. (11) Importantly, these studies all provided e-health 'on top of' usual care, not as a replacement of routine outpatient visits. This is important because the full potential of e-health technologies, including the potential of cost reduction may only be reached by adjusted care pathways with the replacement of care that is not necessary when e-health is delivered. (12) Moreover, these studies typically did not assess the effect of e-health on self-care (defined as the decision and strategies undertaken by the individual in order to maintain life, healthy functioning and well-being (13)), while this is important because education and skills-training with e-health tools will primarily enhance self-care. (14) Obviously, such a patient reported outcome is more difficult to measure and interpret than outcomes such as hospitalisations or mortality. For example, self-care scales do exist, e.g. the European Heart Failure Self-Care Behaviour Scale (one of the self-care scales most often used), but there is no consensus on what is a clinical relevant score or change on its scale. (15)

Thus, there are still some questions to be answered about e-health in HF:
(1) There is a need for studies which quantify the effects of an e-health adjusted care pathway, including replacement of routine HF outpatient consultations, and self-care as a major outcome.
(2) The clinically relevant threshold and change in score of the European Heart Failure Self-Care Behaviour Scale should be assessed.
(3) The worldwide known and freely accessible 'heartfailurematters.org' website needs an evaluation. It is also an example of an e-health tool, and it is currently available in nine languages, providing comprehensive HF information for people with HF and their cares.
(4) The cost-effectiveness of both an e-health adjusted care pathway and the website heartfailurematters.org should assessed.

In this thesis, we aim to answer the aforementioned issues with the following specific questions:

- What is the worldwide uptake of a freely accessible website heartfailurematters.org e-health tool with HF information (chapter 2)?
- What can be considered as a clinically relevant threshold and change in patient reported self-care outcomes in HF (chapter 3)?
- What is the effect of an e-health adjusted care pathway, replacing routine consultations with e-health, on self-care, hospitalisations and mortality in stable HF patients (chapter 5)?
- What is the effect of the website heartfailurematters.org on self-care, hospitalisations and mortality in stable HF patients if added to care as usual provided at the HF outpatient clinic (chapter 5)?
- What is the short-term cost-effectiveness of the website heartfailurematters.org, and an e-health adjusted care pathway, replacing routine consultations with e-health (chapter 6)?
- Do participants in e-health trials differ from non-participants (chapter 7)?

In chapter two of this thesis we describe the background, objectives, worldwide use, lessons learned and future directions of the ESC/HFA heartfailurematters.org website. In chapter three, the interpretability of the European Heart Failure Self-Care Behaviour Scale (EHFScB) scale is studied, i.e. the clinical relevance of individual scores, and changes within these scores. In chapter four, the study design of the e-Vita HF trial in detail is presented. In chapter five, the main results of the e-Vita HF trial are presented evaluating the effect of i) the website heartfailurematters.org, and ii) an e-health adjusted care pathway, replacing routine consultations with e-health, on self-care, hospitalisations and mortality in stable HF patients, compared to usual care. In chapter six, we describe the health effects, costs, and cost-effectiveness of the e-Vita HF trial. In chapter seven, we evaluate whether participants in e-health trials differ from non-participants, and also report on the representativeness of the HF patients included in the e-Vita HF study for the HF population at large.
In chapter eight we summarize the main findings of this thesis, elaborate on the most important finding of the e-Vita HF study and discuss the aspects of e-health in HF that might be recommended for implementation in daily practice.

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‘Heartfailurematters.org’, an educational website for patients and carers from the Heart Failure Association of the ESC: objectives, use, and future directions

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Submitted

ABSTRACT

Aims: In 2007, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) launched the information website heartfailurematters.org (HFM website) for patients, their carers, healthcare professionals, and the general public worldwide to provide a practical tool with advice and guidelines on living with heart failure. The website is managed by the ESC at the European Heart House and is currently available in 9 languages. The aim of this study is to describe the background, objectives, use, lessons learned and future directions of the HFM website.

Methods and results: The number of sessions as measured by Google analytics was used to explore the use of the HFM website from 2010 to 2016. Worldwide, the annual number of sessions increased from 416,345 in 2010 to 1,636,368 in 2015. Most users (72-75%) found the site by using a search engine. Desktops and more recently also smartphones were used to visit the website; in 2015 by 50% and 38% respectively.

Conclusion: Although, increasingly used, the HFM website has not reached its full potential yet: less than 2 million users are visiting the website in contrast to an estimated 23 million people with heart failure worldwide. The uptake and use could be further improved by a continuous process of qualitative assessment of users' preferences, professional helpdesk facilities, and comprehensive information technology and promotional support.

INTRODUCTION

In 2004, members of the Board of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) met with representatives of the pharmaceutical, device and diagnostic industry. In light of the increasing prevalence of heart failure (HF) (1), combined with the unmet need for adequate education of patients, families and their caretakers (2, 3), the discussions focused on the importance of providing a readily available, user-friendly information tool. The proposal emerged for developing an attractive website with information on living with HF in easily understood lay terms and informative animations. Considering the complex nature of the HF syndrome with its multiple causes along with the variety of available life-style adjustments and treatments (4), it seemed logical to use the Internet to provide information. The challenge was to create and promote a user-friendly website targeting a large and heterogeneous population, frequently with little knowledge of, or experience with the Internet.

A group, which consisted of HF cardiologists, primary care physicians, HF nurses, HF patients, pharmacists and lay people from across Europe was established to develop the content and the design of the website. The attractive Uniform Resource Locator 'URL' of heartfailurematters with its double meaning was chosen. The original funding was provided by the HFA along with 22 industry sponsors. A professional agency specialized in building web-based healthcare education, Litmus MME (based in London), was chosen to work with the HFA in creating the site.

After 2 years of preparation and development, the www.heartfailurematters.org (HFM website) was officially launched in September 2007 in English by the Information Technology (I.T.) Department of the European Heart House. In subsequent years other languages were launched and HFM website is currently available in eight additional languages: French, Spanish, German, Russian, Dutch, Greek, Arabic and Portuguese. Swedish is due to be completed during 2016. Each new translation was prepared and validated by a task force from that country. The French, Spanish and German sites were launched in 2008, the Russian and Dutch sites in 2012, the Greek and Arabic sites in 2014, and the Portuguese site in 2015. Between 2014 and 2015 the format and design of the HFM website was completely renewed to make the site more attractive and easier to navigate, in line with modern technological standards and user preferences.

The aim of the HFM website is to provide a user-friendly educational tool for the large and diverse population of patients with HF and their carers so they better understand HF, make appropriate life-style modifications and understand the importance of effective treatment options.

DESIGN

The HFM website provides independent information, and is consistent with the ESC guidelines on HF. (4) Importantly, the websites solely contains essential information on HF, its management, and avoids 'cutting edge' controversial material that could provoke any disagreement between patients and their healthcare providers. The scientific content of the site is the responsibility of the HFM core group, under the auspices of the HFA. The HFM core group has monthly telephone conferences, 3 face-to-face meetings annually and periodically reviews the site content to assure consistency with current practice. Technical issues, lay-out and content are maintained and kept up to date by dedicated personnel at the ESC European Heart House (LA and AC).
The essential information of the HFM website consists of practical information on underlying pathophysiology, diagnosis, lifestyle, self-care, medication, and devices in a readily understood fashion. The information is provided in several formats (e.g. text, animations, movies, downloadable tools), to meet users' preferences. (5)

Content HFM website
The content and the lay-out of the HFM website are shown in table 1. As previously noted, the lay-out was recently renewed. The two (old and new) lay-out formats are shown in the table and described below.
From 2010 to 2014 the homepage (compact and without scrolling option) presented general information on HF, and the avatar 'Anna' (on the left hand side) that could verbally guide users through the website. In the top middle of the site, horizontally, eight subpages provided information on the following subjects: 'understanding heart failure', 'what can your doctor do', 'what can you do', 'living with heart failure', 'for caregivers', 'warning signs', 'FAQ' and 'ask your doctor'.
Every subpage provided a subdivision of other pages with more detailed information on the topic. For example, under 'understanding heart failure' a page presented 'symptoms of heart failure' or 'common tests for heart failure'. The upper right corner of the website provided 'useful tools' such as a printable monitoring chart (e.g. to record bodyweight, blood pressure, current medications regularly). In addition, original animations explaining HF and patients' and caregivers' experiences (in video format or text) were available. After renewing the lay-out in 2014 to 2015, all features (avatar, access to subpages, animations and useful tools) are provided on one comprehensive homepage (with scrolling option). In addition, the bottom of the homepage shows two new features: i) a poll to collect opinions of HFM website users on a topic (the topic changes every four months), and ii) an invitation including a link to a facebook page on which views and experiences with other patients, families and caregivers can be shared.

Table 1. Content of the HFM website in the period 2010 to 2016*

 2010-2014  2014-2016	*Homepage with subpages (number of pages within subpage)* 1. Understanding heart failure (9) 2. What can your doctor do (8) 3. What can you do (6) 4. Living with heart failure (10) 5. For caregivers (7) 6. Warning signs (11) 7. FAQ (1) 8. Ask your doctor (11)
 2010-2016	*Avatar 'Anna' could optionally guide people through the website*
 2010-2016	*Animations* 1. How the normal heart works 2. What goes wrong in heart failure 3. How the heart and the body compensate in heart failure 4. How heart failure works causes fluid accumulation 5. How a heart attack can cause heart failure 6. How abnormal heart valves can cause heart failure 7. How vasodilators work in heart failure 8. How diuretics work in heart failure 9. How medical devices work in heart failure
 2010-2016	*Useful tools* 1. Symptoms and events diary 2. Monitoring chart 3. Warning signs 4. Appointment record 5. Medicine chart
 2010-2016	*Patient and caregivers videos*
 2014-2016	*A poll, to select opinions of HFM website users on heart failure topics*
 2014-2016	*Link to a facebook page to share views and experiences with other patients, families and caregivers*

*HFM website = www.heartfailurematters.org

USE OF HFM WEBSITE

This section provides statistics on the use and trends in use of the HFM website from different angles: how often is the site visited and does it differ per language or country, through what channels do users find the site and what devices are used to access the site? In addition, search terms (i.e. queries) used by visitors to (potentially) find the site are presented.

Methods and data analysis

Google Analytics (GA) was used from January 1st 2010 to January 1st 2016 to gain insight into the use of the HFM website. GA is a web analytic tool. Web analytics is defined as 'the measurement, collection, processing and reporting of Internet data for purposes of understanding and optimizing web usage'. (6, 7) It provides insight in 'what' the user is doing. The users' behavior can reveal necessary changes to the administrator of the website. It offers, however, no insight into the motivation or decision process of the user. (6, 8)

The annual total number of sessions to the HFM website was extracted. A session was defined as an interaction of a visitor with the site. The session ended if i) the visitor left the site, ii) after 30 minutes of inactivity, or iii) at midnight. (6, 8)

Also, the annual numbers of new users (those who have not visited the site before) and returning users (those who previously viewed the site using the same device and browser) were extracted. (8)

For the nine languages and the ESC countries, of which the official native language (9) was one of these nine languages, the annual number of sessions was extracted. The country was determined by the IP address of the user and language determined by the language settings of the users' browser.

The channels by which the visitor to the HFM website was referred to the site were extracted. Examples of channels are links provided by a search engine (= organic channel), other websites (=referral channel), or if the visitor enters the HFM web address directly into their browser or uses a browser bookmark (=direct channel). (8)

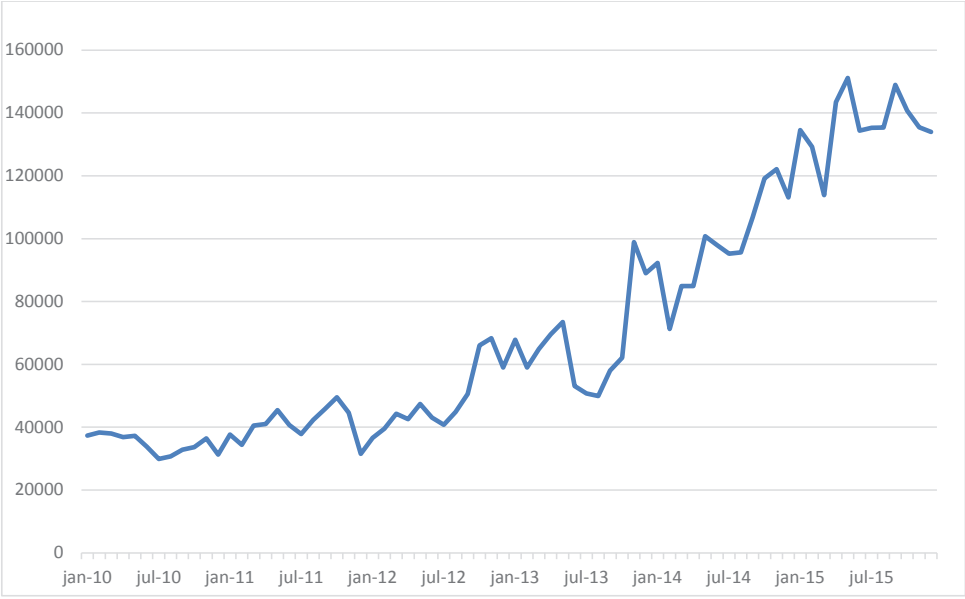
The visits from specific devices (desktop, smartphone and tablet) were registered.

Finally, the top fifteen queries are presented that actually directed users to the HFM website, and the top fifteen queries that users type into Google (related to 'heart failure') whether they directed traffic to the site or not. We only present the English queries. The English version of the website is most often used, thus we assumed that the queries to find the website were more firmly established compared to the other language versions, and therefore a sound example.

RESULTS

The total annual number of sessions of new and returning users to the HFM website, increased from 416,345 in 2010 to 1,636,368 in 2015 (figure 1). Both new and returning users increased in this period: new users from 372,926 to 1,434,985 and returning users from 43,419 to 201,383, respectively.

Figure 1. The annual total number of sessions to the HFM website* from 2010 to 2016

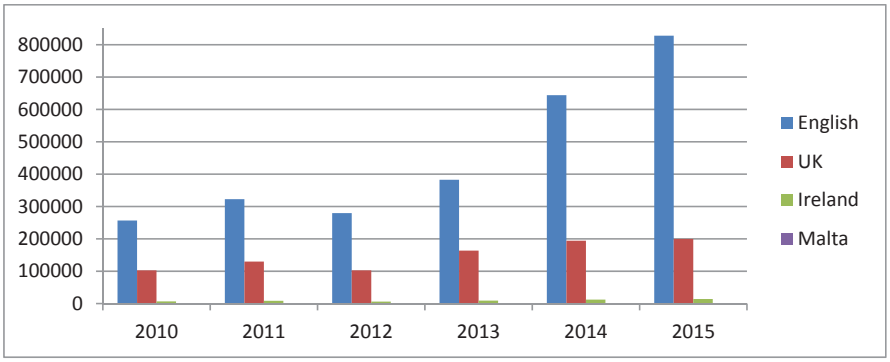


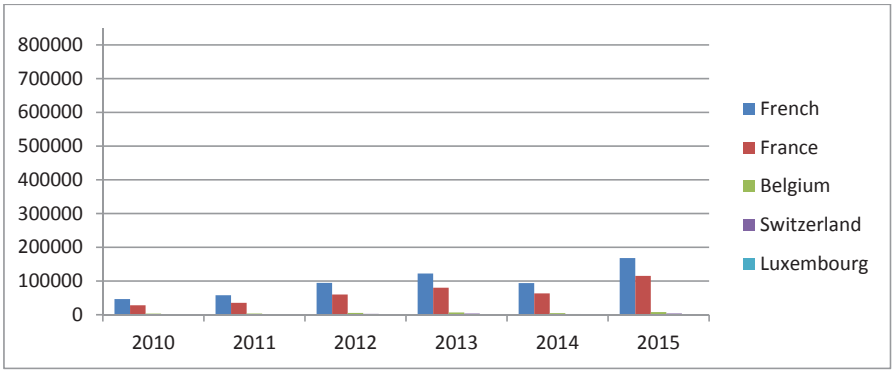
*HFM website = www.heartfailurematters.org

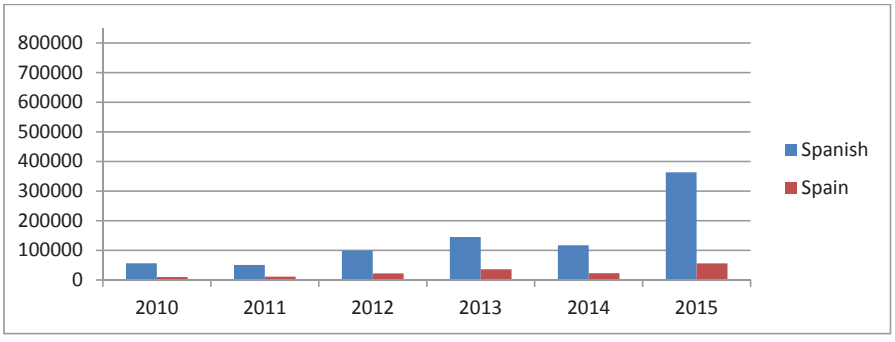
The annual increase in number of sessions in this period was present in all available languages, with the largest increase for English from 256,843 to 827,864 (figure 2). In 2015 the number of sessions decreased for Dutch, German and Russian coinciding with substantial technical problems in these 3 languages (figure 2).

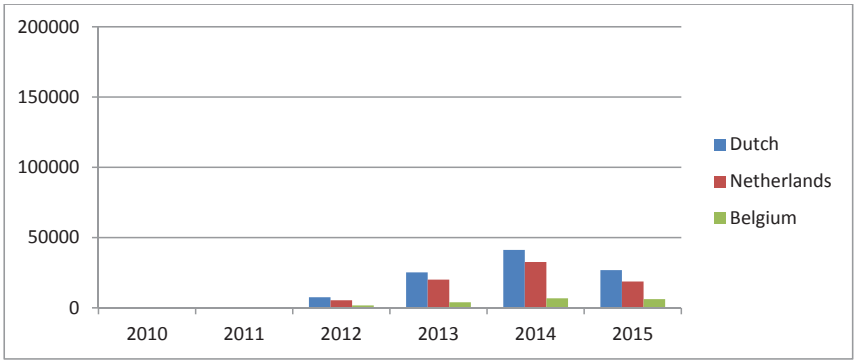
For German, French, Russia and Dutch, the contribution in sessions of the ESC countries covered the total number of sessions of that language. For the other languages, notably for English and Spanish, also countries outside the ESC (e.g. USA and Central and South America respectively) contributed substantially to the total number of sessions.

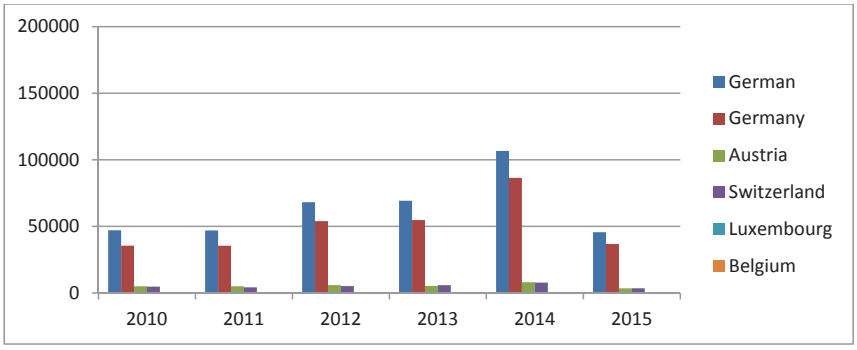
Figure 2. The annual total number of sessions for the English, French, Spanish, German, Russia, and Dutch HFM website* and the contribution to that number of the relevant individual ESC countries, from 2010 to 2016

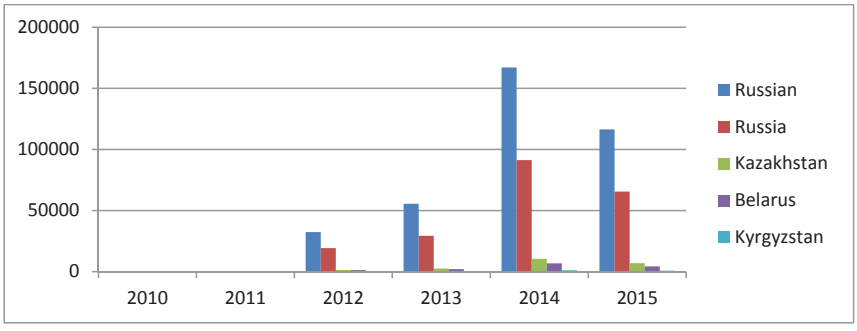








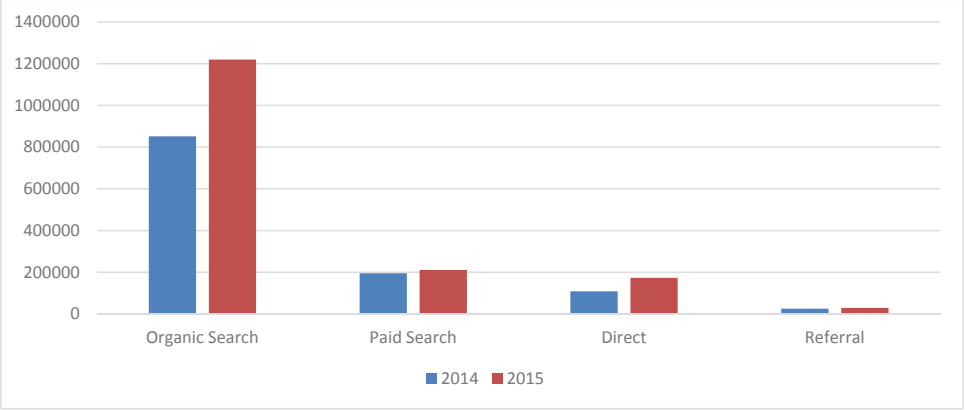




*HFM website = www.heartfailurematters.org

The largest number of users (72% in 2014) found the website by clicking on an organic search listing, followed by users arriving at the site through a paid search advert (16%), direct (9%), and referral (2%) (figure 3). This order remained over the years, but the frequency of sessions per search type increased.

Figure 3. Channels by which the user of the HFM website received the link from 2014 to 2016, frequency in number of sessions



HFM website = www.heartfailurematters.org
Organic search = finding a website by performing a search on a search engine
Paid search = finding the website by clicking on a 'paid for advert' on Google
Direct = access the website directly by typing the URL into the browser or using a bookmark saved in the users' browser
Referral = getting on the website from a link on another site

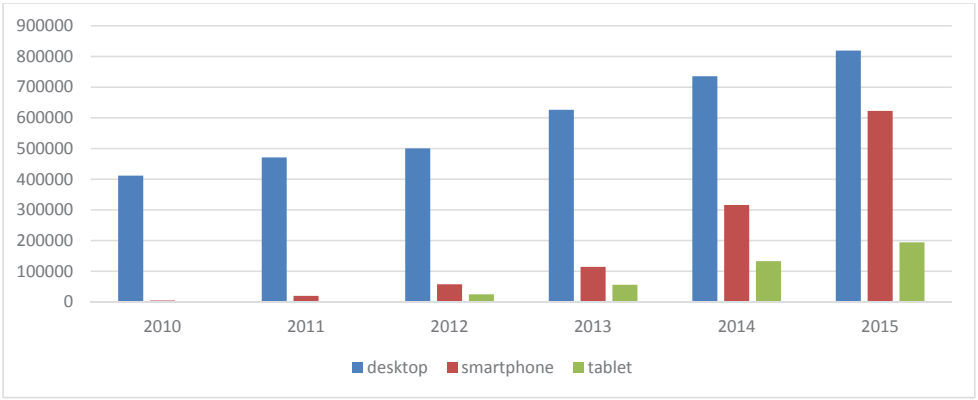
The number of sessions conducted on a desktop, smartphone and tablet device increased over the years, with a rapid increase of the smartphone (figure 4). In 2015, 50% of the sessions were conducted by desktop, 38% by smartphone and 12% by tablet.
From 2015 to 2016 the HFM website was found by users following search terms related to HF such as HF stages, HF symptoms and how to check blood pressure (table 2).
Queries related to 'heart failure' on Google, but not (necessarily) directing the users to the HFM website are less HF specific such as blood pressure and heart attack.

Table 2. Top fifteen of queries that direct users to the HFM website, and those relevant for the HFM website at Google

Queries that direct users to HFM website	Impressions (clicks)
digitalis	20 341 (132)
heart failure stages	11 951 (385)
heart failure symptoms	10 188 (108)
symptoms of heart failure	8390 (68)
how to take blood pressure	7849 (113)
how to check blood pressure	7411 (251)
signs of heart failure	7263 (63)
vasodilators	5598 (25)
how the heart works	4571 (67)
swollen stomach	4083 (59)
heart attack causes	3557 (27)
causes of heart attack	3483 (41)
how does the heart function as a pump	3458 (18)
causes of heart disease	3055 (21)
how does the heart work	3053 (674)
Queries relevant for HF on Google	**Average monthly searches**
blood pressure	550 000
hypertension	368 000
heart attack	301 000
high blood pressure	301 000
normal blood pressure	301 000
low blood pressure	246 000
congestive heart failure	201 000
chest pain	165 000
blood pressure chart	165 000
chf	165 000
heart attack symptoms	135 000
diuretic	135 000
blood pressure checker	135 000
heart disease	110 000
high blood pressure symptoms	110 000

HFM website = www.heartfailurematters.org
Average monthly searches = average number of times people searched for the exact search term
Impressions= the number that any URL the HFM website appeared in Google's search results viewed by the user, not including paid AdWords search impressions.
Clicks = the number of clicks on the HFM website from the potential audience when one of the URLs of the site appears in the search results.

Figure 4. Devices used to access the HFM website* from 2010 to 2016, frequency in number of sessions



*HFM website = www.heartfailurematters.org

LESSONS LEARNED SO FAR

The use of the site substantially increased over time with eventually 1,636,368 sessions in 2015. However, given that HF affects a conservative estimate of 23 million (10) people worldwide and less than 2 million users visiting the HFM website, there is still room for improvement.

An important lesson is that, extensive, preferably daily technical I.T. support is required to maintain a website and keep it updated. Technical deficiencies hinder users to optimally navigate through the website and have a major impact on its use. The decrease in sessions in German, Dutch and Russian in 2015 can easily be explained by a 'bug' existing for six months during the conversion of the old to the new lay-out. A main issue was that the URL that was used to show the HFM website in the native language was not converted to the URL of the new lay-out, with as a result, that visitors were sent to the old, no longer available HFM website. This resulted in a sharp decrease in i) the number of sessions, and ii) visibility in search engines, because the site did not anymore appear on the first page of search engine results, but on page 2 or higher. In the beginning of 2016 this bug was detected and repaired.

Another important lesson is that search engine optimization is more critical if a website is available in multiple languages, as cross-language retrieval by search engines is poor. (11) Besides, I.T. support, continuous professional promotional support is important for search engine optimization. Especially, linking other professional disease management sites to the HFM website is important. Permission from these sites to link to our website was often rapidly obtained, the technical work required was an obstacle and involved more time and personnel than anticipated.

Also, search engine optimization by establishing an infrastructure for promoting the website at a national level by national HF and/or cardiac societies and healthcare professionals soon after the launch should have been more encouraged and financially supported. It has become clear that recommendation of the site by healthcare professionals (e.g. cardiologists, HF nurses, general practitioners) is an effective way to increase accessibility. (10, 11)

Already from the very beginning, there was much enthusiasm from non-English speaking countries for the HFM website. We were able to fund translations into eight other languages. However, the amount of work involved to completely translate the site into new languages was underestimated. Particularly, translating the various audio contents of the site was challenging (obtaining patients' and caregivers' videos in local language has not yet been done because of logistical difficulties related to privacy issues). Retrospectively, we rolled out individual versions too quickly. Focus should have been placed on properly maintaining and improving the quality of the website (e.g. removing bugs) in the existing languages before adding new languages.

FUTURE STRATEGIES

We continually try to further improve and modify the website to meet the objectives of the website and serve the users. We also currently investigate in the e-Vita heart failure randomized trial the effect of the HFM website on self-care, HF knowledge, user satisfaction, and hospitalizations and mortality. (12) Finally, daily technical I.T. support is put into place to check the website and the languages for bugs, and aiming to solve them before harm is done.

Accessibility of the website or how easy it is to locate a website could be further improved. More effort should be put into search engine optimization to increase the chances for patients and carers to find the website. We should put effort in keeping the HFM website on the first page of search engine results if search terms such as 'heart failure' and those mentioned in table 2 are used. Importantly, this should be the case for all nine languages knowing that people tend to search the Internet in their native language. (11)

Also professional promotion of the website is a key component, supported by a 'back-up' team to collect information on the different national infrastructures (e.g. local patient, healthcare professional organisations), create promotional proposals, and be responsible for their implementation in the different countries.

The present analysis used GA data solely, and provides an overview of a HFM website's usability and potential problems. (13) One of the future strategies will be a more thorough analysis of the use of the website by other usability techniques such as interviews, expert opinions, think aloud (asking participants to verbalize their thoughts as they move through the website). (13, 14) These methods help to elucidate motivations or decision processes

of the users that cannot be provided by GA. Think aloud interviews are part of the e-Vita heart failure trial (12) and are the first step understanding users preferences and eventually improve the website further. Alongside, a helpdesk should be created where 'bugs' and suggestions can be reported by users of the website. This information can also be used to optimize the performance of the website continuously.
Finally, insight in demographic data of a representative sample of users of the HFM website would be informative to 'phenotype' those actually visiting the website. This will also help to improve the website.

CONCLUSION

The www.heartfailurematters.org is widely used, with ever increasing visiting numbers. The uptake and use could be further improved by a continuous process of qualitative assessment of users' preferences, professional helpdesk facilities, I.T. and promotional support. Our experience should be helpful in the design and development of future medical education websites for lay persons.

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3

Interpretability of the European Heart Failure Self-care Behaviour scale

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Submitted

ABSTRACT

Objective: The European Heart Failure Self-care behaviour scale (EHFScBs) is a valid patient-reported questionnaire to measure self-care behaviour of heart failure (HF) patients. We assessed the interpretability of the EHFScBs.

Methods: We used data of 1,023 HF patients. Interpretability refers to the clinical meaning of the score and its changes over time. We operationalised interpretability by evaluating distributions of EHFScBs scores across relevant HF subgroups by eyeballing, by testing the risk on hospitalisations and mortality of a plausible threshold, and by determining a clinically relevant minimal important change (MIC). The scale score ranges from 0-100, with a higher score meaning better self-care. A threshold of ≥70 was defined as adequate, and <70 as inadequate self-care.

Results: The EHFScBs scores were similarly normally distributed among the subgroups with a mean between 57.8 (SD 19.4) and 72.0 (SD 18.0).
The 464 HF patients with adequate self-care had significantly less all-cause hospitalisations than the 559 patients with inadequate self-care.

Conclusion: The degree of self-care showed to be independent of relevant HF subgroups. A single threshold of 70 accurately discriminates between patients with adequate and inadequate self-care.

INTRODUCTION

The European Heart Failure Self-care Behaviour Scale (EHFScB scale) is a patient-reported outcome (PRO) questionnaire to measure self-care behaviour of heart failure (HF) patients. Self-care behaviour reflects actions undertaken to maintain life, healthy functioning, and well-being. (1, 2)

The EHFScB scale has been psychometrically tested (1-3), i.e. its validity (=does it measure what it should measure?), reliability (=is it free of measurement error?), and responsiveness (=is it sensitive to changes?) have been evaluated. (4-6) Besides these test characteristics, the interpretability is an important and recently acknowledged PRO characteristic that – as for many other PROs – has not yet been evaluated for the EHFScB scale. (4, 5) Interpretability refers to the possible clinical meaning of the score results, and its changes over time. (4, 5) Despite the fact that the EHFScB scale is widely used as an outcome in clinical trials, the clinical relevance of the score results and of the changes in the score over time are unknown. Moreover, a threshold for 'adequate self-care' related to relevant outcomes is unknown.

Knowledge of the interpretability of the EHFScB scale score is urgently needed to properly value results of clinical trials in HF using this PRO as an outcome, and to address whether the scale is suitable for evaluation of health care interventions. (7)

Our overall study aim was to assess the interpretability of the EHFScB scale in a cohort of patients with HF. The study questions were:

1. What is the distribution of the scores of the EHFScB scale in HF patients?
2. Can a threshold of the EHFScBs scores distinguish between adequate and inadequate self-care in HF patients?
3. What is the clinically relevant minimal important change in EHFScBs score in HF patients?

METHODS

Cross sectional and longitudinal data of participants of the "Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure" (COACH study) (8) was used. Missing values of variables were imputed by multiple imputation using SPSS version 21.0 (Armonk, NY: IBM Corp). (9)

Study population

The COACH study was a 3-arm multicentre, randomized clinical trial in patients with HF, comparing the effects of moderate and intensive disease management support to usual care. Details of the COACH study have been published elsewhere. (8, 10) Patients, 18 years or older, were included during hospitalization for HF and were symptomatic (based on New

York Heart Association functional classification 'NYHA', class II-IV). Important exclusion criteria were i) inability to complete the questionnaires, ii) invasive procedures (e.g. cardiac surgery or intervention) within the last 6 months or planned within the next three months, and iii) ongoing evaluation for heart transplantation. During the hospitalisation patients were randomly allocated to one of the three arms.

All patients received 'routine' care by their cardiologist common in the Netherlands. This included a visit at the outpatient clinic within 2 months after hospital discharge, and every 6 months after that. Patients in the two intervention arms with extra support were visited by a HF nurse during hospitalisation and received education and extra support. They were also scheduled for additional visits at the outpatient clinic. Patients in the most intensive support arm had, on top of the latter, weekly contact by telephone with the HF nurse in the first month after hospital discharge and monthly contact afterwards including 2 home visits. (8, 10)

Patients were followed for 18 months. At baseline, patient characteristics (e.g. age, educational level, depressive symptoms) were measured. At baseline and after 12 months all participants filled out questionnaires on self-care behaviour (EHFScBs) and HF-related quality of life (Minnesota Living with Heart Failure Questionnaire (MLHFQ)). The NYHA classification was collected from the hospital medical file. (8) In addition, at these time points, B-type natriuretic peptide (BNP) levels were measured, and hospitalisations and death were retrieved from the hospital medical files at the end of the study and adjudicated by a blinded endpoint committee.

EHFScB scale

The EHFScB scale includes both self-reported consulting (e.g. 'if I gain weight I contact a doctor or nurse') and adherence to regimen behaviours (e.g. 'I exercise regularly'). It consists of nine items that are scored on a 5 point Likert scale resulting in a standardized score from 0-100 (every item is given an equal weight) with a higher score meaning better self-care. (1, 3) The EHFScB was developed in 2003 (2) and reduced to a 9-item scale (EHFScB-9) in 2009. (1)

Operationalizing interpretability

We operationalised interpretability by evaluating ***distributions*** of EHFScB scale scores across relevant subgroups, by evaluating whether a plausible ***threshold*** in the EHFScBs scores can distinguish between adequate and inadequate self-care, and assessing a clinically relevant ***minimal important change (MIC)***. (5, 11-14)

Information on how the EHFScBs scores of the study population and its relevant subgroups are ***distributed*** is important for the interpretation of the scores. It provides information on whether the population and its subgroups have a low or a high score on average, and if the

scores are distributed over the whole range of the scale, or clustered. We considered the following subgroups as clinically relevant and possibly related to self-care: age (<60, between 60 and 80, ≥80 yrs), gender (female, male), marital status (having a partner, single), level of education (primary, secondary and vocational, middle and higher education), disease severity measured with the NYHA classification (I, II, III, IV), duration of HF (0-3 mnths, 3-6 mnths, 6 mnths – 1 yrs, 1-2 yrs, 2-3 yrs, 3-5 yrs, >5 yrs), LVEF (<20, between 20 and 35, ≥35), concurrent depressive symptoms (not depressed, depressed), and patient's knowledge on HF (insufficient, sufficient). (5)

To determine whether a ***threshold*** in scores distinguishes between adequate and inadequate self-care we defined this as 70, based on the threshold of another self-care scale the 'Self-Care of Heart Failure Index' (SCHFI). For the SCHFI a threshold for adequate self-care was set at ≥70 based on narrative accounts. (15) The SCHFI and the EHFScB scale measure similar constructs/aspects, and have the same standardized score (from 0-100). (3)

To assess the ***MIC*** we used the change in EHFScBs score between baseline and 12 months. For this analysis we included patients with an EHFScBs score of < 70 at baseline, since these patients still have room for improvement in self-care. To help 'quantify' the change in score over time we used an anchor-based method. In this approach, one or more anchors (=external criterion, a kind of reference standard) are used, which is an easy to interpret variable that is clearly related to prognosis, either improvement or deterioration. In this case the anchor-based method assesses which changes in self-care correspond with the clinically relevant changes in the anchor variable. (5) Anchors used were: Health status, HF-related hospitalisations, and BNP as biomarker level of left ventricular wall stress. (16)

Details on the anchors

We used the MLHFQ to measure HF-related health status. It is a validated questionnaire including 21 items on patient perceptions on the effects of HF on their physical, psychological and socioeconomic functioning on a 6-point scale with higher scores indicating worse quality of life. (17) Based on the A-HeFT study, the following clinically relevant changes were determined: improved (≥-5 units), unchanged (-4 until 4 units), and worse (≥ 5 units). (18) HF-related hospitalisation was defined as unplanned overnight stay in a hospital due to progression of HF or directly related to HF. (8) Categories used for HF related hospitalisation were no hospitalisation, 1, 2, 3, 4, 5, and ≥ 6 hospitalisations. Finally, we used the level and change of B-type natriuretic peptide (BNP). We hypothesized that adequate self-care results in maintenance of volume homeostasis by appropriate (diuretic) drug use, and thus, lower left ventricular wall stress and BNP values. (16, 19) An increase and decrease in BNP level of 25, 25 to 50 or more than 50% were considered clinically relevant. (20)

Analysis of the EHFScB score

For the ***distributions*** of the EHFScB score we used data at 12 months follow-up. This data, and not baseline data, was used to avoid homogeneous results in self-care due to recent hospitalisation.

At 12 months follow-up most participants were at home, and consequently not reminded on a daily basis by the nurses to perform self-care behaviours like taking medication. Using data collected at 12 months provides probably a more realistic view on self-care, than using data collected at baseline. The distributions are presented by histograms.

We tested the discriminative value of the ***threshold*** 70 by dividing the study population in two groups at baseline, into those with a score below or ≥ 70 on the EHFScB scale. Participants considered as having adequate self-care (EHFScB ≥ 70) were compared with those with inadequate self-care (EHFScB <70) regarding all-cause mortality and all- and HF-related hospitalisations at 12 months by a Chi square test.

To determine the ***MIC***, first the change in self-care as measured with EHFScB scale was correlated with the change over one year in the three anchors. If the correlation was sufficient (at least r=0.3/-0.3 (21)) the MIC was calculated for the separate anchors. To calculate the MIC we applied the most frequently used method (14) which is called the 'mean change method'. In the mean change method the MIC is calculated from the mean change in the score on the EHFScB scale in patients whose values are 'minimally importantly changed' between baseline and 12 months follow-up according to the anchor.

RESULTS

The mean age of the 1023 HF patients was 70.8 (SD 11.4) years, and 63% were men. The mean LVEF was 33.8% (SD 13.7), and 96% of the patients were classified as NYHA II or III at discharge from the hospital. Most (61%) were living with a partner, and reported a low education (86%) (table 1).

Distribution and threshold

The scores on the EHFScBs for the 1023 HF patients were normally distributed with generally higher scores (mean 65.3 (SD 20.3)) meaning better self-care. The EHFScB scores among most subgroups (gender, NHYA class, LVEF, duration of HF, depressive symptoms, educational level and marital status, (figure 1)) were distributed similarly. The mean score per subgroup ranged from 57.8 (SD 19.4) to 72.0 (SD 18.0). However, small differences in age groups were present with a mean score in self-care of 72 (SD 18.0), 66 (SD 20.2) and 59 (SD 20.1) for <60, between 60 and 80 and ≥80 years of age respectively. Differences were also present in high and low HF knowledge groups with a mean of 67 (SD 20.0) and 60 (SD 20.2) respectively.

Table 1. Baseline characteristics of the 1023 COACH study* participants

	N	%
Mean age in years (SD)	1023	70.8 (11.4)
Male sex	639	62.5
Mean LVEF† (SD)	1023	33.8 (13.7)
NYHA‡		
2	514	50.2
3	471	46.0
4	38	3.7
Length of HF§ in months	1023	Median 3.6 (IQR 0.7-46.5)
Depressive symptoms, CES-D¶ score ≥ 16	405	39.6
Marital status		
Living with a partner	619	60.5
Single	404	39.5
Educational level		
Primary education	359	35.1
Secondary education, lower and secondary vocational education	516	50.4
Middle and higher education	148	14.5
Mean knowledge in HF§ (SD)	1023	11.0 (2.3)
Management randomised to		
Care as usual	338	30.0
Basic support	341	33.3
Intensive support	344	33.6

*COACH = Coordinating study evaluating Outcomes of Advising and Counseling in Heart Failure
† LVEF= Left Ventricular Ejection Fraction
‡ NYHA= New York Heart Association functional classification
§ HF= heart failure
¶ CES-D score= Center for Epidemiological Studies Depression scale

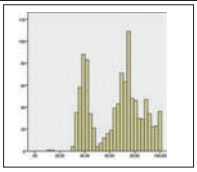
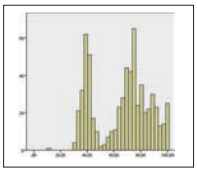
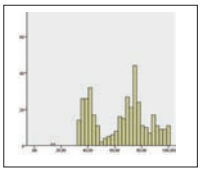
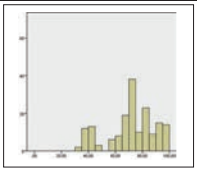
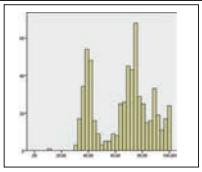
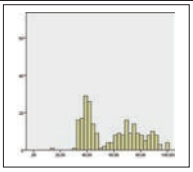
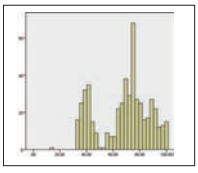
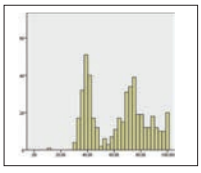
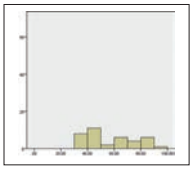
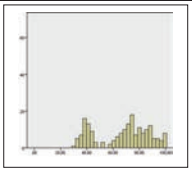
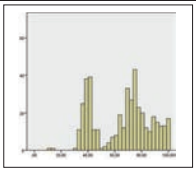
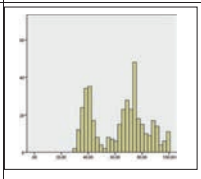
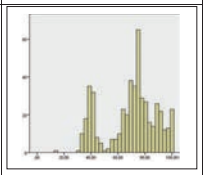
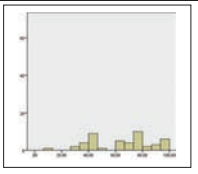
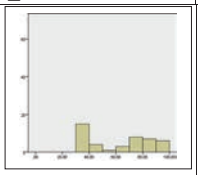
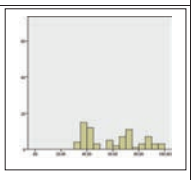
Regarding the threshold, HF patients with adequate self-care had significantly less hospitalisations due to all-cause as compared to the patients with inadequate self-care; OR 0.77 (95% CI 0.60-0.99) (table 2).

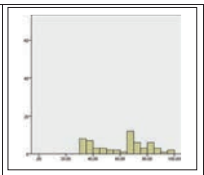
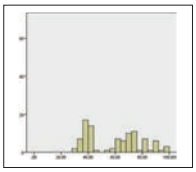
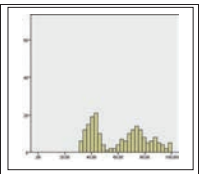
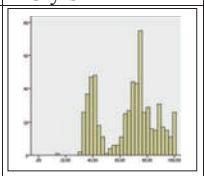
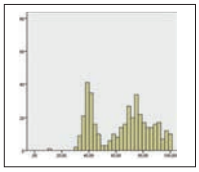
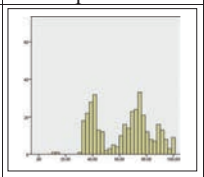
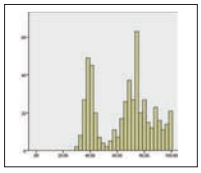
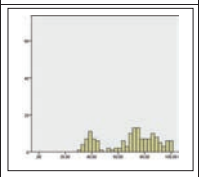
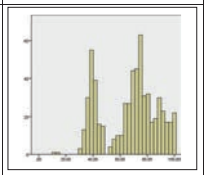
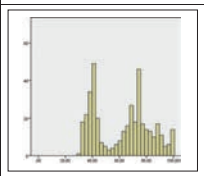
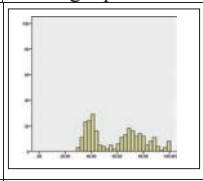
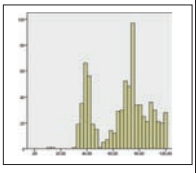
Table 2. The relation between adequate (EHFScB score ≥ 70) versus inadequate self-care (EHFScB score <70) and all-cause mortality, and hospitalisations during 12 months follow-up in 1023 patients with HF*

	Adequate self-care (N=464)	Inadequate self-care (N=559)	
	N (%)	**N (%)**	**P-value†**
All-cause mortality	117 (25.2)	155 (27.7)	0.37
All-cause hospitalisations	241 (51.9)	326 (58.3)	**0.04**
HF-related hospitalisations*	113 (24.4)	147 (26.3)	0.48

* HF= heart failure
† P-value calculated with the Pearson Chi-Square

Figure 1. Distribution of the EHFScBs* scores at 12 months, in relevant subgroups of HF† (Y-axis= number of patients, X-axis= EHFScB score (0-100))

Study sample				
	EHFScBs*			
Gender				
	Male	Female		
Age				
	<60yrs	between 60 and 80yrs	≥80yrs	
NYHA‡				
	II	III	IV	
LVEF§				
	<20	between 20 and 35	≥35	
Length of HF† in months				
	0-3 months	3-6 months	6 months - 1yr	1-2 yrs

Length of HF† in months				
	2-3 yrs	3-5 yrs	>5 yrs	
Depressive symptoms based on CES-D score¦				
	Not depressed	Depressed		
Educational level				
	Primary education	Secondary education, lower and secondary vocational education	Middle and higher education	
Marital status				
	Having a partner	Single		
HF† knowledge				
	Insufficient	Sufficient		

* EHFScBs= European Heart Failure Self-care Behavioural scale
† HF= heart failure
‡ NYHA= New York Heart Association functional classification
§ LVEF= Left Ventricular Ejection Fraction
¦ CES-D score= Centre for Epidemiological Studies Depression scale

MIC

Because the correlation coefficients for the change in the EHFScB scale and the concomitant change of the anchors did not exceed 0.3 (poor correlation), the MIC could not be calculated. Figure 2 shows the associations by scatterplots with the concomitant correlation coefficient (=r).

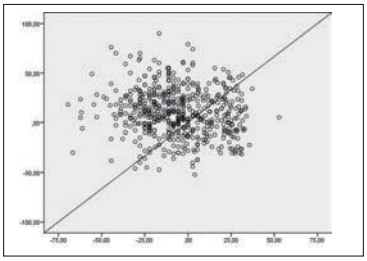
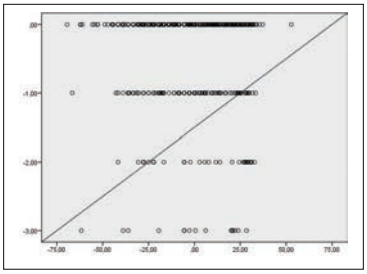
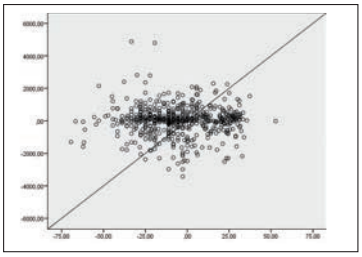
	Inadequate self-care
Change in MLHFQ score†	 R=-0.127
	Change in EHFScB score
Change in number of HF related hospitalisations§	 R=-0.133
	Change in EHFScB score
Change in BNP‡	 R=-0.004
	Change in EHFScB score

Figure 2. Correlations of change in the EHFScBs* score during 12 months on the X-axis and the anchors on the Y-axis

* EHFScBs= European Heart Failure Self care Behavioural scale
† MLHFQ = Minnesota living with Heart Failure Questionnaire
§ HF= heart failure
‡ BNP= B-type natriuretic peptide (pg/mL)

DISCUSSION AND CONCLUSION

The scores on the EHFScBs for the study sample were overall normally distributed with similar score distributions among subgroups. The mean score per subgroup ranged from 57.8 (SD 19.4) to 72.0 (SD 18.0). HF patients with adequate self-care (EHFScB score ≥70) had significantly less all-cause hospitalisations than patients considered to apply inadequate self-care (EHFScB score <70); OR 0.77 (95% CI 0.60-0.99). The correlation of the change in the EHFScB scale over 12 months with the change in results of the used anchors was poor, and did not allow computing the clinically minimal important change (MIC) for the EHFScB score. The distribution of the EHFScBs scores in most relevant subgroups was similar to the distribution of the whole study population. This means that despite gender, depressive symptoms, LVEF, NYHA class, education, marital status, or duration of HF self-care is similarly distributed ranging from 11 to 100 with a mean score of 65.3 (SD 20.3). However, if patients are older their self-care is probably lower. Also, if their HF knowledge is insufficient their self-care is somewhat lower as well. The latter findings are in line with the literature. (22)

Our study showed that the degree of self-care seems to be independent of relevant HF subgroup characteristics. However, one could argue that these findings could be less homogeneous in other study samples. It is common that trial participants as in the COACH trial (=RCT) are a selective sample and may not represent HF patients with very low self-care. (23, 24) In addition, our study population, had been hospitalized and educated previously which most probably also contributed to a homogeneous population.

We were surprised to find no correlation of the EHFScBs with any of the anchors. For example, we would have expected HF-related hospitalisations to be correlated as a previous review found that disease management programs enhancing patient self-care activities reduced HF-related hospitalisations significantly. (25) We do not have an explanation for this.

As a consequence of this lack of correlation, we could not calculate the MIC. A MIC would have provided useful information. For example, if we would have found that self-care decreased by 2 points (on average) following every additional hospitalisation, we could have concluded that because hospitalisation is a major event, a decrease of 2 points on the EHFScB scale is also a clinically relevant major decrease.

Strengths and limitations

Before analysis, missing values were imputed with multiple imputation with SPSS. This is a strength of our study as analyses can be performed on the entire dataset and not only on the participants with complete data. In addition, results are more trustworthy than with complete case analysis. (26, 27)

Unfortunately, in our data we did not have information on other appropriate anchors. For example, measures closer to the concept of self-care, like compliance to HF treatment regimens. (1, 28) Therefore we could not incorporate these measures in our analysis.

Practice implications

The variance of the distribution across relevant subgroups was limited in the COACH study population. Differences in distributions may be more pronounced in another HF population. The threshold of 70 can be used in designing studies, evaluating interventions, and informing health policy makers. (7)

CONCLUSIONS

Scores on the EHFScBs are equally distributed in relevant subgroups of patients with HF included in a trial. For now, it is uncertain whether a clinically relevant change can be defined. A threshold of '70' can be used to discriminate between adequate and inadequate self-care.

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4

Effectiveness of an interactive platform, and the ESC/HFA heartfailurematters.org website in patients with heart failure: design of the multicentre randomized e-Vita heart failure trial

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Tiny Jaarsma, Arno W Hoes, and Frans H Rutten

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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 with usual care. In addition, we will determine whether the ESC/HFA (European Society of Cardiology/Heart Failure Association) 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 randomized 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 outpatient clinic. In total, 414 patients managed in 10 Dutch HF outpatient clinics or in general practice 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, hospitalisation, and its duration as captured by hospital and general practitioner registries, use of and user satisfaction with the HFM website, and cost-effectiveness.

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

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 healthcare budget. (2) This problem is growing because of the ageing of the population and improved care following acute cardiac events (3), while healthcare budgets are cut.
Educational programs focussed on patient self-care can result in a reduction in both HF-related and all-cause hospitalisation rates. (4) However, these programs demand considerable human resources, and are not cost saving. (5) In The Netherlands, the majority of hospitals have HF outpatient clinics with HF nurses providing care. Because these programmes require a great deal of time and money, 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 outpatient clinics) would reduce the time investment of healthcare workers and thus reduce healthcare 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 hospitalisations prevented. With e-health, for example a website with information targeted at patients and their family/carers, such as the website heartfailurematters.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 outpatient 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 outpatient 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

The study comprises a three-arm parallel multicentre randomized 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 outpatient clinic. Four hundred and fourteen patients with established diagnosis HF managed in 10 Dutch HF outpatient 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 1 year.

Study population and recruitment

Heart failure patients from the outpatient clinic will be asked to participate by HF nurses. For eligibility criteria, see table 1.

Invitation to participate in the study of patients known to have HF in primary care will be done by a poster and reply-card at the offices of the general practitioners (GPs). Eligibility criteria for HF patients primarily managed in general practices are identical to those of patients recruited from the outpatient clinics. For inclusion in the study, these patients will be referred to the nearest participating HF outpatient clinic to allow for baseline measurements and randomization, and when necessary to confirm the diagnosis of HF and provide 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 outpatient clinic, since it was not feasible for GPs to become accustomed to and maintain the e-Vita platform for potentially just 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 healthcare providers outside the primary care setting with whom they are not familiar. Secondly, these patients should be referred to the outpatient 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 outpatient clinic before any study procedure is undertaken.

Randomisation

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

Table 1 Inclusion and exclusion criteria

Inclusion criteria
Diagnosed with HF (independent of EF) for at least 3 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; EF, ejection fraction; ESC, European Society of Cardiology.

Study arms

Arm 1: Allocated patients receive usual care from the cardiologist, HF nurse, and other healthcare workers at the HF outpatient 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 3 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 to 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 factors other 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 1 day, +2 kg in three consecutive days,-3 kg in 1 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 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 decisions with the patient, and, when necessary, after consulting 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 ask the patient to visit the outpatient clinic, ask the GP to make a home visit, or ask the patient present himself at the general practice or hospital.
In The Netherlands, all community-dwelling persons are enrolled 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 co-morbidities and medication, including in those with HF managed at the outpatient clinics. Therefore, involvement of the GP in this intervention arm is crucial. (9, 10) On the e-Vita platform, co-morbidities and medication will be kept up to date by the patient, as will be 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 co-morbidities 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 co-morbidities 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 5h 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 European Society of Cardiology (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 1-4 face-to-face consultations per year; one with the cardiologist and 1-3 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.

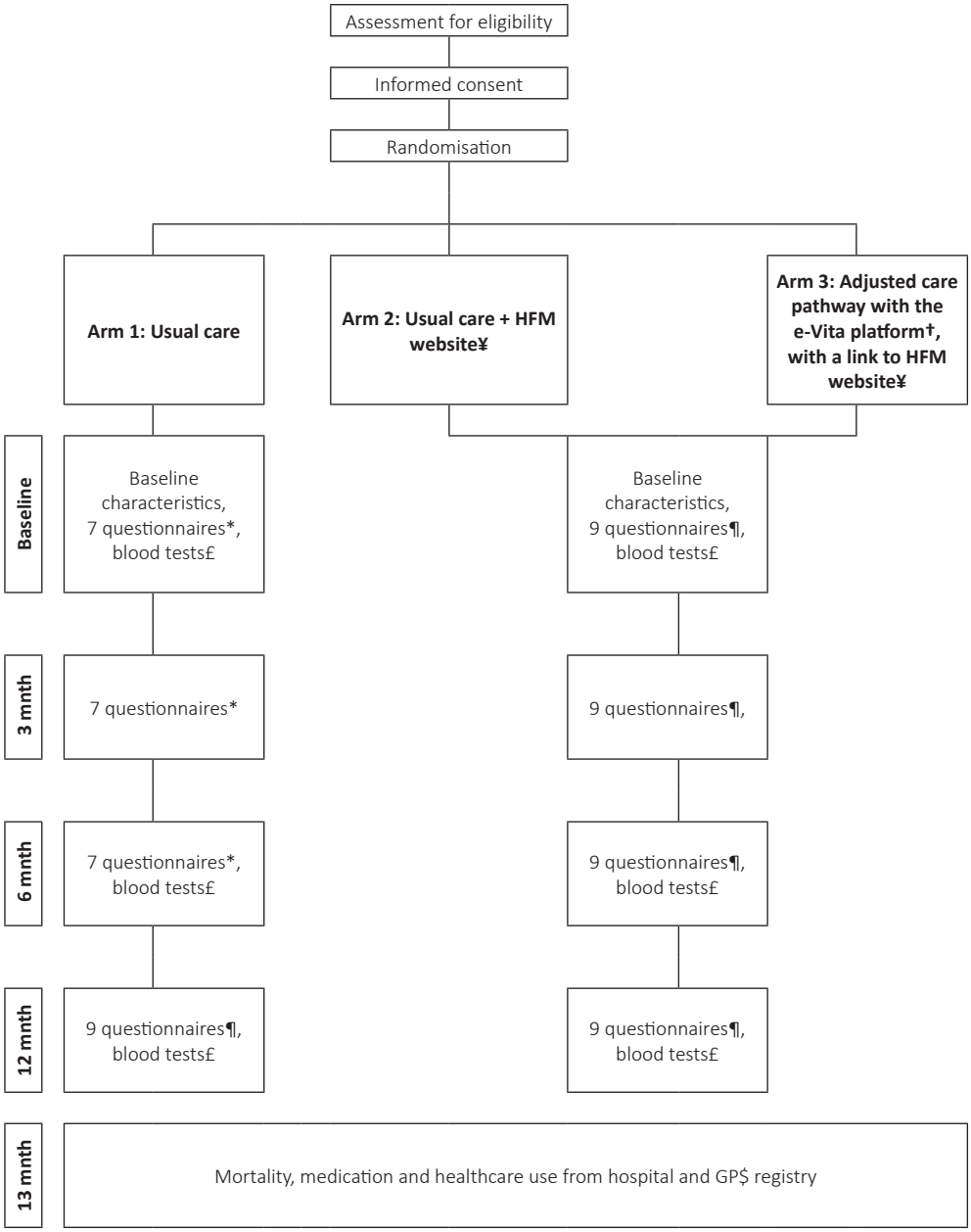

Figure 1. Data collection
*7 questionnaires-EHFScB, SF36, EQ-5D, MLHFQ, DHFk, QoHF and VAS, ¶9 questionnaires-EHFScB, SF36, EQ-5D, MLHFQ, DHFk, QoHF, VAS, WUS and 'use of website', $GP=general practitioner, †e-Vita platform= interactive platform for disease management and a link to the HFM website, ¥HFM website= 'www.heartfailurematters.org', and £blood tests=(NT-pro)BNP and eGFR.

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 ~60 min to complete these. For participants in arm 2 and 3, the use of and the user satisfaction with 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 QoL and probably reduce healthcare costs. Therefore, we chose self-care as the primary outcome (see table 2).

Table 2 Questionnaires used in the study

Related to primary outcome	
European Heart Failure Self Care Behaviour Scale (EHFScB scale)	Self-care
Related to secondary outcomes	
Short-Form health survey with 36 questions (SF36)	Health-related quality of Life
EuroQol five Dimensions (EQ-5D)	Health-related quality of Life
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	Disease-specific health-related quality of Life
Use of website	Frequency, length and parts visited by website visits
Website User Satisfaction (WUS)	Website user satisfaction
Visual Analogue Scale (VAS)	Patient satisfaction about their HF and the HF care
Dutch Heart Failure knowledge scale (DHFk)	Disease-specific knowledge
Questions on heart failure (QoHF)	Disease-specific knowledge

HF, heart failure.

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 (i) 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 Heart Failure questionnaire (MLHFQ); (21) (ii) the use of the website and its user satisfaction measured by the 'use of website' and the website user satisfaction (WUS) (22) questionnaire; (iii) disease-specific knowledge measured with the Dutch Heart Failure knowledge scale (DHFk) (23) and 'questions on heart failure (QoHF)' questionnaire; (iv) 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; (v) N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, renal function [estimated Glomerular Filtration Rate (eGFR)]; and (vi) cardiovascular-related mortality, HF-related mortality, cardiovascular-related hospitalisations, HF-related hospitalisations 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 healthcare use [e.g. (telephone) consultations, medication, all-cause mortality, hospitalisations, 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 analysis of variance (ANOVA) to detect a difference of 0.5-2.0 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) Unstandardized scores of the EHFScB scale are used.

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 2 (usual care plus HFM website) and arm 1 (usual care), and between arm 3 (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 ~46 subjects per outpatient clinic (including patients recruited from the general practices) resulting in ~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 the effects at 3 and 6 months will also 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) 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 hospitalisations 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 healthcare 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 co-morbidities 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 for 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 co-morbidities. 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 healthcare 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 healthcare professionals are aware of the allocation of the patient, they could influence healthcare use (e.g. face-to-face contacts, hospitalisations) related to a specific study arm. We, however, expect this potential bias to be limited because the healthcare professionals are not involved in development of the platform and do not receive any financial incentive to take part in the study.

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5

Effectiveness of the ESC/HFA website heartfailurematters.org and an e-health adjusted care pathway in patients with stable heart failure: results of the 'e-Vita HF' trial

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Submitted

ABSTRACT

Background: Incorporation of electronic health support (e-health) in patients with heart failure (HF) has been suggested to make healthcare more efficient while empowering patients.

Aims: To assess the effect on self-care of (1) the ESC/HFA website heartfailurematters.org (HFM website) on top of usual care, and (2) an e-health adjusted care pathway with replacement of routine HF nurse consultations in stable HF patients.

Methods: In a three-group parallel-randomised controlled trial in stable HF patients from nine Dutch HF outpatient clinics, we compared two interventions (HFM website and an e-health adjusted care pathway) to usual care. The primary outcome was self-care measured with the European Heart Failure Self-care Behaviour Scale (EHFScB scale). Secondary outcomes were health status, mortality, and hospitalisations.

Results: In total, 450 (150 per group) patients were included. The mean age was 66.8 (SD 11.0) years, 74.2% were male, and 78.8% classified as NYHA I or II at baseline. After 3 months follow-up, the mean score on the self-care scale was significantly higher in the groups using the website and the adjusted care pathway compared to usual care: 73.5 vs. 70.8 (difference 2.7, 95%CI 0.6 – 6.2), and 78.2 vs. 70.8 (difference 7.4, 95%CI 3.8 – 9.4), respectively. The significant effect attenuated during the following 9 months until no differences after one year between the groups (difference -0.6, 95%CI -3.7 – 3.4, and 3.4 95%CI -0.7 – 6.4, respectively). Quality of life and HF knowledge showed the same pattern as was observed in self-care. Other secondary outcomes did not clearly differ between the groups.

Conclusion: Both the heartfailurematters.org website, and an e-health adjusted care pathway improved self-care in HF patient on the short-term, but this effect attenuated during the following 9 months. Continuous updating of e-health facilities could be helpful to sustain effects over longer time.

Trial registration: ClinicalTrials.gov NCT01755988

INTRODUCTION

Heart failure (HF) is a chronic progressive disease, with an increasing prevalence with age. It has a major impact on health status, hospitalisations, and on the healthcare budget. (1, 2)
Due to aging of the population and demand on healthcare resources, e-health interventions to improve relevant patient outcomes, such as self-care, are heavily promoted. (3)
Multidisciplinary programs targeted at improving patient self-care (activities such as taking medication as prescribed, seeking healthcare in case of weight gain, engagement in regular exercise) can have a beneficial effect on hospitalisation, mortality, and HF-related quality of life. (4) These programs, however, demand considerable human resources, and are time-consuming. Efficient incorporation of electronic health (e-health) blended with existing care by replacing routine consultations could reduce the time investment of HF nurses per patient, creating time for the care of more patients, and improve patient-relevant outcomes. (3) Moreover, e-health programs may be more patient-friendly as they enable self-care activities at a time and place convenient for the patients, and reduces travel time to the hospital.
An example of an e-health tool is the website 'heartfailurematters.org' (HFM website) with information targeted at patients and their family/carers to improve self-care. Although the site is used intensively and translated in several languages, its effect on patient outcomes has never been evaluated.
Earlier studies assessed the effect of e-health tools (mostly telemonitoring) as part of disease management programs. Some showed promising, but others neutral results in patients with HF. (5, 6) These interventions were predominantly evaluated 'on top of' usual care. In view of the anticipated shortage in healthcare facilities, evaluation of e-health interventions with replacement of routine HF outpatient visits seems more relevant.
For our study we deliberately wanted to evaluate an interactive platform for HF disease management (e-Vita platform) with telemonitoring facilities, replacing routine consultations. We also wanted to evaluate the effect of the HFM website. Both were compared to usual care with as primary outcome self-care and as secondary outcomes health status, hospitalisations and all-cause mortality.

METHODS

Study design

A three-group parallel multicentre randomised pragmatic trial with 1:1:1 group allocation was performed. Patients in group 1 received usual care (UC), in group 2 usual care plus the HFM website (HFM), and in group 3 an e-health adjusted care pathway with the e-Vita platform including a link to the HFM website (EACP).

Four hundred and fifty HF outpatients were recruited from nine Dutch HF outpatient clinics between October 2013 and December 2014. Patients were followed-up for one year. Patients were individually randomised by computerised block randomisation (maximum of nine patients per block) to one of the three groups.
Details of the design of the e-Vita HF study have been published elsewhere and a summary of the main design features is presented below. (7)
The study was conducted according to the principles stated in the current Declaration of Helsinki (8) and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO) and approved by the medical ethics committee of the University Medical Center Utrecht, the Netherlands (number 12/456).

Study population

HF patients were eligible to participate if (i) aged 18 years or over, and diagnosed with HF for at least three months; (ii) capable to fill out questionnaires, and perform blood pressure measurements and weighing (by standing on a weighing scale); (iii) they had access to internet and e-mail, with basic user skills (or their spouses or carers); and (iv) able to read and understand Dutch.
Written informed consent was obtained during the first study visit at the HF outpatient clinic before any study procedure was undertaken.

Study groups (table 1)

Usual Care group (UC): Allocated patients received usual care from one of the 9 HF outpatient clinic teams, at least constituting a cardiologist and HF nurse. Usual care consisted of on average four routine consultations a year (typically 3 with the HF nurse, and 1 with the cardiologist).
HeartFailureMatters.org website group (HFM): Participants received, 'on top of' usual care, information about the HFM website and 10 minutes instruction on its use from the HF nurse at the start of the study. During each routine consultation, patients were encouraged by the HF nurse to use the website, and individually experienced barriers were explored and solved by the nurse. Additionally, participants received a leaflet with useful information about the HFM website, and every three months a reminder by e-mail to use the website.
E-health Adjusted Care Pathway group (EACP): Participants in this group followed an e-health adjusted care pathway. They received identical initial information on the use of the HFM website as the participants of HFM. In addition, the HF nurses instructed the patients and their caretakers on how to use the e-Vita platform with telemonitoring facilities. Patients learned to record at a fixed time point body weight, blood pressure and heart rate on a daily basis (or individually adjusted to a lower frequency if stable). All participants used a standardized user-friendly weighing scale and blood pressure/heart rate device. The results

of these vital parameters were automatically forwarded to the e-Vita platform. At the start of the study, uniform pre-specified alert limits for the values of body weight, blood pressure, and heart rate were set: 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)). To reduce unhelpful alerts, we encouraged the HF nurses to adjust these limits in shared decision with individual patients, and when necessary after consultation of the cardiologist or general practitioner (GP) of the patient.

If recordings of body weight, blood pressure, and/or heart rate were outside these limits or if measurements were not recorded, the HF nurse received an alert via the e-Vita platform. If deemed necessary, the HF nurse contacted the patient by phone to explore symptoms, and possibly adjust the individual management, ask the patient to visit the outpatient clinic, or visit the GP practice.

On the e-Vita platform, comorbidities and medication were kept up to date by the patient, and checked by the HF nurse, who also encouraged the patients to keep it updated. Also, patients received monthly reminders by e-mail. Finally, no routine face-to-face consultations with the HF nurse were scheduled, but if needed the patient could always contact the nurse.

Table 1. Components of the interventional groups and care as usual

Characteristics	Usual care	Website	E-health adjusted care pathway
Face-to-face contact HF nurse	+	+	-
Measurement of vital signs			
Body weight	RC	RC	regularly
Blood pressure	RC	RC	regularly
Heart rate	RC	RC	regularly

RC= routine consultation
Regularly= most often daily but at least once in the 2 weeks

Measurements and outcome parameters

Demographic and disease-specific characteristics were collected at baseline.

Questionnaires were completed by patients at baseline, and after 3, 6 and 12 months. Blood tests were performed at baseline, and after 6 and 12 months. Electronic medical files of the HF outpatient clinics and the GP were reviewed after 12 months follow up.

The primary outcome was patient's self-care. Self-care was defined as the decision and strategies undertaken by the individual in order to maintain life, healthy functioning and well-being. (9) Self-care was measured with the European Heart Failure Self-care Behaviour (EHFScB) scale. (10) The EHFScB scale includes both self-reported consulting (i.e. 'if shortness of breath increases, leg/feet are more swollen, I gain weight and/or experience fatigue I

contact doctor or nurse'), and adherence to regimen behaviours (i.e. 'I weigh myself every day', 'I limit the amount of fluids', 'I exercise regularly', 'I eat a low salt diet', 'I take my medication as prescribed'). It consists of nine items which are scored on a 5 point Likert scale resulting in a standardized score from 0-100 (every item is given an equal weight) with a higher score meaning better self-care. (10, 11)

Secondary outcomes were (i) health-related disease-specific quality of life (hrQoL) measured with the Minnesota living with HF questionnaire (MLHFQ), scoring between 0-105 with lower scores meaning better hrQoL (12), (ii) disease-specific knowledge measured with the Dutch Heart Failure knowledge scale (DHFk), scoring between 0-15 with higher scores indicating more knowledge (13), (iii) patient satisfaction about the HF care measured with a Visual Analogue Scale, scoring between 0-100 with higher scores meaning higher satisfaction, (iv) N-terminal pro B-type natriuretic peptide (NT-proBNP) levels, (v) renal function (estimated Glomerular Filtration Rate (eGFR)), (vi) all-cause mortality, (vii) cardiovascular related mortality, (viii) HF-related mortality, (ix) all-cause hospitalisations, (x) cardiovascular related hospitalisations, (xi) HF- related hospitalisations, and (xii) number of days of HF hospitalisations as captured by hospital and GP registries. The cause of death was assessed by an independent adjudication committee constituting a GP and two cardiologists who were unaware of the patient's allocation.

Statistical aspects

The sample size calculation was based on an alpha of 0.05 and a power of 80% with ANOVA to detect a difference of 0.5 (HFM vs. UC) and 2.0 (EACP vs. UC) in self-care behaviour measured with the EHFScB scale. The estimated mean (SD) EHFScB scale score in HF patients is 20 (5.54), based on unpublished data from a previous study. (14) Based on the aforementioned assumptions, we required at least 414 patients (138 per group) for the study.

We performed an intention to treat analysis. Missing values were imputed by multiple imputation methods. (15) The overall difference between the groups in self-care at 3, 6 and 12 months was determined with an ANCOVA. Differences per comparison, between HFM vs. UC and EACP vs. UC were calculated with multiple linear regression models. Results of the crude regression model were presented. If residuals (i.e. an important assumption of a linear regression model) of the model were more sound with adjustment for the baseline values of self-care, the results of the adjusted model were presented as well.

Differences in hrQoL, HF knowledge, patient satisfaction about the HF care, NT-proBNP and eGFR determined after 3 and/or 6 and 12 months were also calculated with multiple linear regression models. Differences in mortality (disease-specific and all-cause) and hospitalisations (disease-specific and all-cause) were analysed with a Cox-regression model, and the mean duration of HF hospitalisations with a multiple linear regression model. For all secondary outcomes results of the crude model were presented.

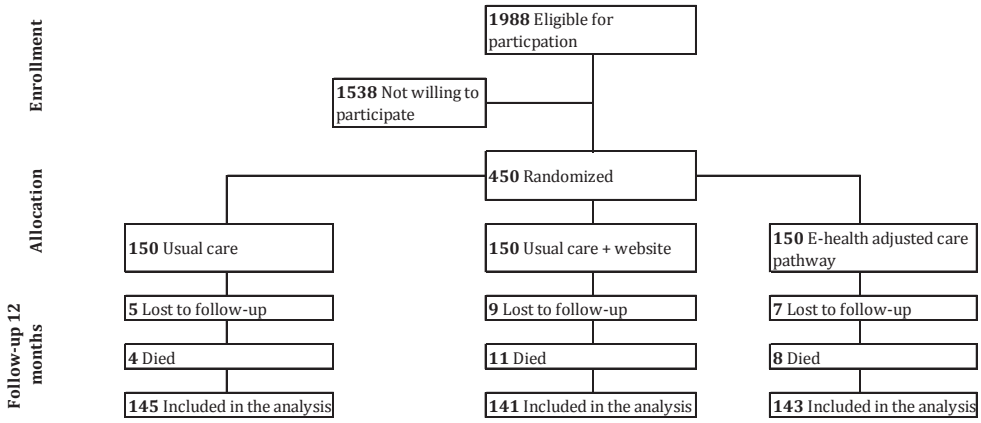
Analyses were performed with SPSS version 21.0 (Armonk, NY: IBM Corp).

RESULTS

Demographics

From the 1,988 invited patients, 450 (23%) consented to participate and were randomized (150 patients per group) (figure 1). Mean age of the participants was 66.8 (SD 11.0) years and 74.2% were male. At baseline, 78.8% was classified as NYHA I or II, and the mean left ventricular ejection fraction (LVEF) was 35.7 (SD 10.8) (table 2). Most baseline characteristics did not differ between the three study groups after the randomisation, although, there were more smokers in UC (19%) than in the HFM and EACP group (12%, and 14% respectively). The proportion of patients in NYHA I was higher in EACP (49%) than in the UC and HFM (40%).

Figure 1. Flow chart



Primary endpoint self-care

At baseline, the mean self-care on the EHFScB scale was 70.6 (SD 14.6) in the UC, 69.3 (SD 16.4) in the HFM, and 72.0 (SD 16.0) in the EACP. After 3 months, there was a significant (overall p-value <0.001) difference in self-care between de study groups; HFM vs. UC and EACP vs. UC; mean 73.5 vs. 70.8 (difference 2.7, 95%CI 0.6- 6.2), and 78.2 vs. 70.8 (difference 7.4, 95%CI 3.8 – 9.4), respectively. The significant effect attenuated during the following 9 months, with at 6 months HFM vs. UC mean 74.7 vs. 74.2, and EACP vs. UC 78.6 vs. 74.2 respectively (overall p-value 0.070), and at 12 months HFM vs. UC mean 72.1 vs. 72.7, and EACP vs. UC 76.1 vs. 72.7, respectively (overall p-value 0.184) (see table 3).

Table 2. Baseline characteristics of the 450 participants in the e-Vita HF study divided over the three groups

			N[a]	Usual care (150)	Website (150)	E-health adjusted care pathway (150)
Demograpics	Age (years)			66.9 ± 11.6	66.7 ± 10.4	66.6 ± 11.0
	Male			109 (72.7)	112 (74.7)	113 (75.3)
	BMI (kg/m^2)			28 ± 4.1	28.1 ± 5.1	27.9 ± 5.6
	Education level		449	149		
		Low		34 (22.8)	31 (20.7)	34 (22.7)
		Middle		66 (44.3)	67 (44.7)	59 (39.3)
		High		49 (32.7)	52 (34.7)	57 (38.0)
	Marital status (married/partner)			110 (73.3)	123 (82.0)	107 (71.3)
			449	149		
	Living situation (independent, with others)			111 (74.5)	124 (82.7)	114 (76.0)
	Smoking (currently)			29 (19.3)	18 (12.0)	21 (14.0)
			432	145	143	144
	Self-care			70.6 ± 14.6	69.3 ± 16.4	72.0 ± 16.0
			432	145	143	144
	HF related QoL (median ± IQR)			23.0 ± 32.5	24.0 ± 31.0	23.0 ± 27.8
Heart related characteristics	Duration of HF (months)			40.6 ± 36.0	45.3 ± 42.4	38.5 ± 35.7
			432	142	145	145
	LV ejection fraction %			36.2 ± 10.0	35.2 ± 11.1	35.6 ± 11.2
	NYHA Classification		428	143	144	141
		I		57 (39.9)	57 (39.6)	69 (48.9)
		II		55 (38.5)	53 (36.8)	46 (32.6)
		III		24 (16.8)	17 (11.8)	17 (12.1)
		IV		7 (4.9)	17 (11.8)	9 (6.4)
	Hypertension			70 (46.7)	62 (41.3)	65 (43.3)
	Acute coronary syndrome			71 (47.3)	69 (39.3)	72 (48.0)
	Stable angina pectoris			28 (18.7)	26 (17.3)	20 (13.3)
	Atrial fibrillation			54 (36.0)	68 (45.3)	66 (44.0)
	Other heart rhythm disorders			44 (29.3)	44 (29.3)	42 (28.0)
	Valvular heart disease			58 (38.7)	66 (44.0)	57 (38.0)
Other comorbidities	CVA			20 (13.3)	9 (6.0)	25 (16.7)
	Hypercholesterolemia			43 (28.7)	52 (34.7)	51 (34.0)
	Diabetes mellitus			39 (26.0)	36 (24.0)	40 (26.7)
	Renal failure			22 (14.7)	23 (15.3)	24 (16.0)
	COPD			30 (20.0)	44 (29.3)	36 (24.0)
Blood samples			287	95	98	94
	NT-proBNP in pg/ml (median ± IQR)			474.6 ± 1313.6	902.5 ± 1317.0	629.2 ± 1078.4
			402	133	132	137
	eGFR (MDRD)			65.7 ± 22.1	68.6 ± 32.9	67.9 ± 25.2
			404	133	133	138
	Urea (median ± IQR)			7.9 ± 5.0	7.8 ± 5.0	7.7 ± 5.0
			388	127	129	132
	Haemoglobin			8.6 ± 0.9	8.6 ± 1.1	8.5 ± 0.9
Medication	Diuretics			121 (80.7)	115 (76.7)	100 (66.7)
	MRA			61 (40.7)	66 (44.0)	59 (39.3)
	ACE-i/ARBs			122 (81.3)	115 (76.7)	115 (76.7)
	Beta-blockers			128 (85.3)	123 (82.0)	121 (80.7)
	Oral anticoagulants			71 (47.3)	72 (48.0)	69 (46.0)
	Platelet antagonists			50 (33.3)	49 (32.7)	52 (34.7)
	Lipid lowering drugs			79 (52.7)	81 (54.0)	72 (48.0)

Values are presented as number (%) or mean +/- SD, [a]if not specified N=450, CVA = CerebroVascular Accident (including TIA), COPD = Chronic Obstructive Pulmonary Disease, BMI = Body Mass Index, HF = heart failure, QoL = Quality of Life, NYHA = New York Heart Association Functional Classification, Diuretics = includes loop diuretics, and thiazides, MRA=mineralocorticoid antagonists, ACE-i = Angiotensin-Converting-Enzyme inhibitor, ARBs = angiotensin receptor blockers, eGFR = estimated Glomerular Filtration Rate, and MDRD = formula based on Modification of Diet in Renal Disease Study

Table 3. Overall effect and effect per comparison of a website and an e-health adjusted care pathway on patient self-care after 3, 6, and 12 months, unadjusted and adjusted for self-care at baseline

		Model 1: Unadjusted	Model 1: overall effect between the groups	Model 2: Adjusted for self-care at baseline	Model 2: overall effect between the groups
	Mean	**95%CI**	**P-value**	**95%CI**	**P-value**
3 months			<0.001		<0.001
Usual care	70.8	ref		ref	
Website	73.5	(-0.61- 6.14)		(0.60- 6.22)	
E-health adjusted care pathway	78.2	(4.05- 10.80)		(3.80- 9.43)	
6 months			0.034		0.070
Usual care	74.2	ref		ref	
Website	74.7	(-3.08- 4.21)		(-2.08- 4.38)	
E-health adjusted care pathway	78.6	(0.81- 8.10)		(0.48- 6.94)	
12 months			0.082		0.184
Usual care	72.7	ref		ref	
Website	72.1	(-4.45- 3.21)		(-3.71- 3.44)	
E-health adjusted care pathway	76.1	(-0,39- 7,27)		(-0.74- 6.41)	

Table 4. Effect of a website and an e-health adjusted care pathway on secondary outcomes after 3, 6, and 12 months

Outcomes		3 Months		6 Months		12 Months	
		Median (N=150)	95%CI of the difference between groups	Median (N=150)	95%CI of the difference between groups	Median (N=150)	95%CI of the difference between groups
Patient satisfaction about their HF care (0 = no satisfaction, 100 = maximal satisfaction)	Usual care	75.7	ref	75.5	ref	75.3	ref
	Website	76.1	-6.33- 7.39	75.2	-7.03- 6.48	71.5	-12.32- 1.79
	E-health adjusted care pathway	77.8	-1.32- 12.39	80.5	-0.19- 13.32	71.7	-10.65- 3.46
HF related quality of life (0 = best QoL, 105 = worst QoL)	Usual care	22.8	ref	24.0	ref	26.5	ref
	Website	26.5	-4.42- 4.81	26.0	-5.70- 3.80	28.3	-3.63- 6.08
	E-health adjusted care pathway	19.0	-9.76--0.53*	21.0	-11.90--2.40*	25.5	-7.90- 1.81
Disease-specific knowledge (0 = most insufficient knowledge, 15 = most sufficient knowledge)	Usual care	13.0	ref	13.0	ref	13.0	ref
	Website	13.0	-0.18- 10.49	13.0	-0.19- 0.50	13.0	-0.28- 0.39
	E-health adjusted care pathway	13.0	0.09- 0.75*	13.0	-0.06- 0.63	13.0	-0.14- 0.53
eGFR	Usual care	NA	NA	61.2**	ref	63.7	ref
	Website	NA	NA	60.6**	56.97- 64.37	61.2	56.40- 66.36
	E-health adjusted care pathway	NA	NA	61.2**	57.56- 65.69	68.4	63.07- 73.44
NT-proBNP	Usual care	NA	NA	600.8**	ref	549.0	ref
	Website	NA	NA	651.0**	538.15- 795.32	594.9	496.70- 712.37
	E-health adjusted care pathway	NA	NA	532.8**	436.03- 644.48	486.9	406.48- 583.06

CI = confidence interval, HF = heart failure, QoL=Quality of Life, HF-related quality of life = measured with the Minnesota Living with Heart Failure Questionnaire (MLHFQ), Disease-specific knowledge= measured with Dutch Heart Failure knowledge scale (DHFk), e-GFR and NT-proBNP analysed on a log scale, presented in marginal means (CI) transformed backwards using the exponential function, *significant, **marginal mean, and NA=not measured

Secondary outcomes

After 3 and 6 months, significant differences were observed in hrQoL between EACP and UC (median EACP 19.0 vs. UC 22.8, p-value =0.029 and EACP 21.0 vs. UC 24.0, p-value =0.003), and at 3 months in HF knowledge (Median EACP 13 vs. UC 13, p-value =0.014). This effect attenuated during follow-up, with at 12 months no clear differences between the groups on HrQoL and HF knowledge. A similar, although non-significant, trend was observed for NT-proBNP and eGFR if EACP was compared to UC (table 4).

There was no difference between groups in patient's satisfaction about the received HF care. Finally, there were no clear differences in all-cause mortality (HFM vs. UC HR 2.82 (95%CI 0.90-8.87) and EACP vs. UC HR 2.06 (CI 0.62-6.84)), and hospitalisations (HFM vs. UC HR 0.98 (95%CI 0.70-1.38) and EACP vs. UC HR 0.85 (95%CI 0.59-1.21)) between the groups (table 5). Neither was this the case for disease specific hospitalisations and the duration of HF-related hospitalisations (table 5).

Table 5. Effect of a website and an e-health adjusted care pathway on mortality and hospitalization

Outcomes		N	HR	95%CI of the difference between the groups
All-cause mortality	Usual care	4	ref	ref
	Website	11	2.82	0.90- 8.87
	E-health adjusted care pathway	8	2.06	0.62- 6.84
CV-related mortality	Usual care	3	ref	ref
	Website	9	3.06	0.82- 11.32
	E-health adjusted care pathway	7	2.39	0.62- 9.26
HF-related mortality	Usual care	3	ref	ref
	Website	7	2.39	0.62- 9.24
	E-health adjusted care pathway	3	1.03	0.21- 5.11
All-cause hospitalisations	Usual care	66	ref	ref
	Website	66	0.98	0.70- 1.38
	E-health adjusted care pathway	57	0.85	0.59- 1.21
CV-related hospitalisations	Usual care	22	ref	ref
	Website	29	1.31	0.75- 2.27
	E-health adjusted care pathway	17	0.76	0.40- 1.43
HF-related hospitalisations	Usual care	12	ref	ref
	Website	8	0.65	0.27- 1.60
	E-health adjusted care pathway	7	0.57	0.23- 1.45
Number of days of HF-relatend hospitalisations	Usual care	9*		ref
	Website	8*		-12.58- 17.09
	E-health adjusted care pathway	5*		-29.42- 13.82

HR = hazard ratio, CI = confidence interval, HF = heart failure, CV = cardiovascular, and * = median

DISCUSSION

We observed an improvement in self-care at 3 months when stable HF patients received guidance in the use of the website 'heartfailurematters.org' compared to usual care (mean score on EHFScBs 73.5 vs. 70.8 (difference 2.7, 95%CI 0.6 - 6.2). An e-health adjusted care pathway resulted in an even higher improvement when compared to usual care (mean 78.2 vs. 70.8 (difference 7.4, 95%CI 3.8 – 9.4)). These effects attenuated during the following 9 months, and no clear differences were seen at 12 months between the groups (mean 72.1 vs. 72.7 for the website vs. usual care, and mean 76.1 vs. 72.7 for the adjusted care pathway vs. usual care, respectively). Secondary outcomes such as hrQoL and HF knowledge showed a similar trend, but mortality and hospitalisations did not clearly differ between the groups.

We are the first to evaluate the health effects of the website 'heartfailurematters.org'. Previously, only the very short-term (2 weeks) effect of a website with HF information was evaluated showing a significant effect on self-care knowledge. (16)

Only few studies evaluated the effect of e-health/telemonitoring interventions on self-care. One of these is the recently published Dutch TEHAF study, where the usual care and the study population were comparable with our study, namely HF patients managed in Dutch HF outpatient clinics. The effect of our e-health adjusted care pathway is in line with this TEHAF study, that reported a significant improvement in self-care on the EHFScB scale for the telemonitoring group vs. care as usual at 12 months (17.4 (SD 4.5) vs. 20.8 (SD 5.8), p=<0.001). (17) These unstandardized scores correspond with mean standardized scores on the EHFScB scale of 76.7 and 67.3, which is similar to our EHFScB scale scores at 3 months. The TEHAF study monitored symptoms, HF knowledge, and HF-related behavior, with HF nurse intervening when patients gave high-risk (inadequate) responses. (17) Our study monitored just body weight, blood pressure and heart rate, and HF nurses intervened with lifestyle advices or drug treatment adjustments when reported values fell outside the predetermined limits. The workload related to monitoring in the TEHAF study was, as expected, more with on average 2.20 min per patient per day (18), compared to 1.30 min per patient per day (estimated) in our study. Another telemonitoring study, conducted in Canada showed a statistically significant effect on self-care maintenance (a component of self-care) in the telemonitoring group vs. care as usual (73.3 (SD 11.6) vs. (65.5 (SD 15.8), p=0.03), at 6 months follow-up. Self-care was measured with the SCHFI, another self-care questionnaire from which the standardized scores can be interpreted in the same way as from the EHFScB scale. (11) They evaluated a phone-based monitoring system and asked the patient to measure weight and blood pressure, answer symptom questions and perform an SelfCheck electrocardiogram. (19)

The fact that the adjusted care pathway in our study also increased HF knowledge after 3 months is not surprising as HF knowledge is strongly related self-care. (9) The positive

effect on hrQoL after 3 and 6 months follow-up we found was also observed in previous telemonitoring studies. (20)

We purposely replaced all routine consultations with the HF nurse in the adjusted care pathway group, and indeed fewer HF outpatient clinic consultations took place in the EACP (mean = 2) compared to UC and HFM (mean = 3). This was also observed in other recently published telemonitoring studies conducted in the Netherlands. (21, 22) So, even though more information between the HF nurse and the patient was exchanged (i.e. vital parameters on a daily basis, instead of 3 times per year in care as usual) this did not result in enhanced demand of face-to-face consultations, and this is in contrast to the fear expressed by healthcare providers regarding telemonitoring. Whether the adjusted care pathway really reduces workload and costs in comparison to care as usual and the HFM website group will be reported in the cost-effectiveness analysis of the e-Vita HF study. Importantly, the patient perception of the received care in our study did not significantly differ between the groups suggesting that patients with HF remained equally satisfied with the e-health adjusted care pathway (with less routine consultations with the HF nurse) as with usual care.

Both 'heartfailurematters.org' as the e-health adjusted pathway point to a short-term effect on self-care. Both e-health tools, although, very different in nature, seem to address but not sustain the components necessary to maintain self-care as measured with the EHFScB scale consisting of two components; self-care maintenance (e.g. 'I exercise regularly') and self-care management (e.g. 'if I gain weight I contact a doctor or nurse'). Possibly adding monitoring of the symptom shortness of breath and providing a way of interactive learning like the pre-set questions and dialogues in the TEHAF study (about symptoms, knowledge, and behaviour) can enhance the sustainability of the effect given that the effect in the TEHAF study lasted over 12 months. (17) Possibly, pro-active e-signals or contacts, for example 'triggers' and 'push messages' (i.e. any notification from a smartphone app that displays while that app is not actively in use) could be helpful to improve sustainability. (23) In addition, incorporation of behavioural models in e-health could be key to help sustain the effect on self-care. (24)

E-health applications are rapidly evolving, and often require new procedures and infrastructures every few months. (25) We did not allow these changes to happen in our study because it is in general not accepted to change the intervention during the study. However, it should be reconsidered when evaluating e-health tools, as it would better represent the real world of the modern e-health tool, in this era of rapid ICT growth. (26)

Several strengths and limitations of our study should be mentioned. We were able to include the number of patients as needed based on our sample size calculations which allows us to draw robust conclusions regarding our primary outcome self-care.

Missing data was imputed by multiple imputation techniques, allowing us to analyse the entire dataset, which results in more credible outcomes as was shown by simulation studies. (27)

We also imputed values on self-care in patients who died during the year follow-up, from time of death onwards. To be certain this did not bias our results, we performed a sensitivity analysis excluding patients who died (5.1%), which revealed similar results. A previous analysis showed that our results are certainly generalizable to those who are relatively young and healthy. We do not know if the effect is similar in elderly. (28)

Interpreting our results, one has to realize that in the Netherlands the care delivered by HF outpatient clinics is rather intensive compared to many other European countries with on average 4 routine consultations a year. (29) Therefore, it is a challenge to surpass the effect of usual care on self-care and other outcomes with the interventions and effects of the studied interventions may be (much) larger in more deprived areas. (21, 30)

Moreover, the HFM website is freely accessible since 2012 and even though we explicitly instructed the HF nurses not to encourage this, patients in the usual care group may have visited the site themselves, which could have resulted in a smaller effect (i.e. difference) between the intervention groups and care as usual. Indeed, according to a patient reported questionnaire filled out at the end of the study, 21% of the patients in the UC group had visited the HFM website once or more often. In the HFM and EACP, where patients were stimulated to use the HFM website and received short instructions on how to 'surf' the site, 57%, and 66%, visited the website respectively once or more often.

To conclude, we showed that both the HFM website and e-health platform improved self-care in HF patient on the short-term, but this effect attenuated during the following 9 months. Continuous updating of e-health facilities to help sustain effects over longer time should be considered for evaluation.

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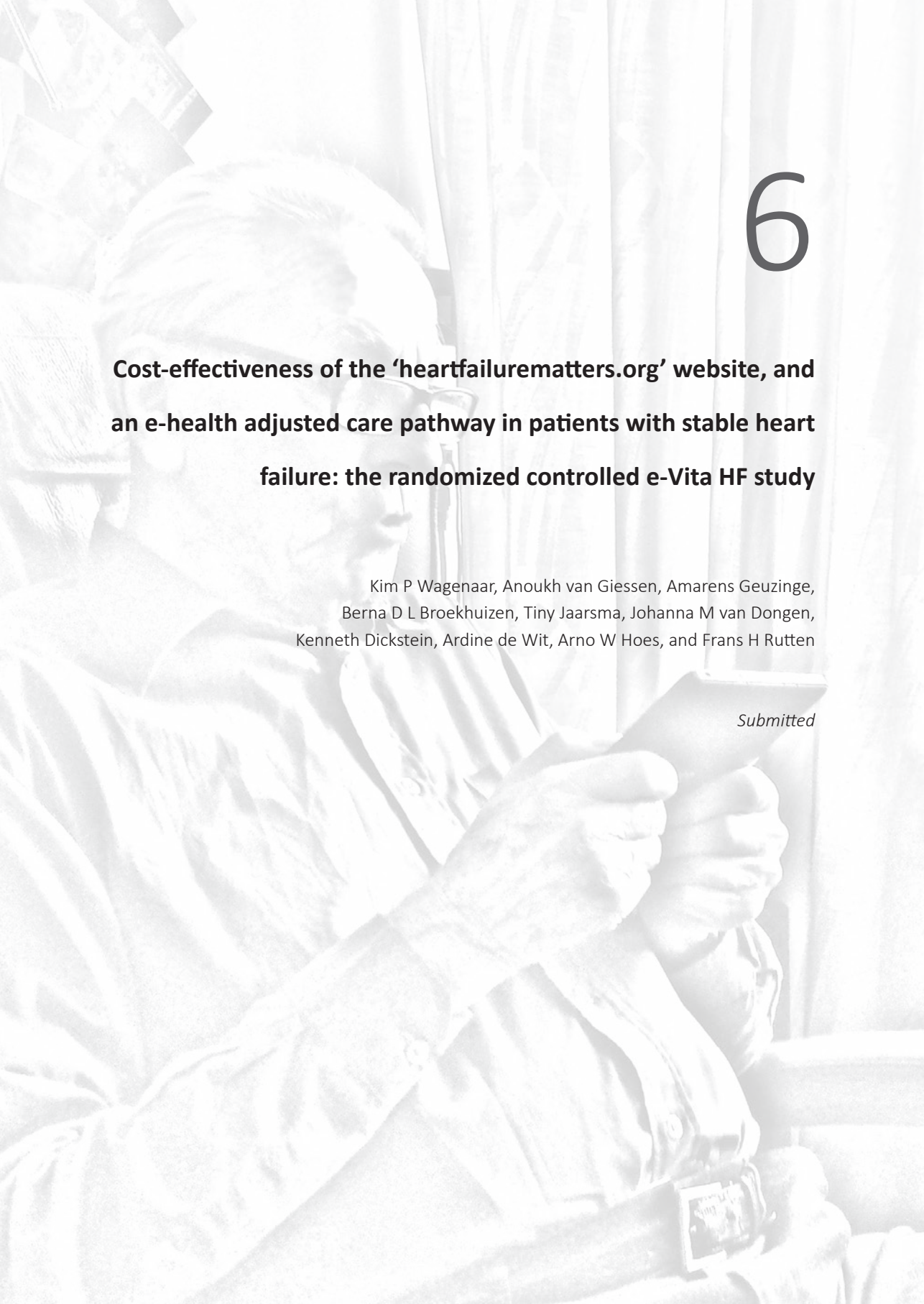

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Cost-effectiveness of the 'heartfailurematters.org' website, and an e-health adjusted care pathway in patients with stable heart failure: the randomized controlled e-Vita HF study

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ABSTRACT

Background: Heart failure (HF) management heavily impacts the healthcare system and budget. Use of electronic health (e-health) may replace routine consultations and thus reduce costs and enhance patient's self-care and well-being.
We aimed to evaluate the cost-effectiveness of the website heartfailurematters.org, aimed at improving self-care by targeting patients and their cares, and an adjusted care pathway with replacement of routine consultations by e-health in patients with HF.

Methods: In Dutch HF outpatient clinics, 450 stable HF participants were randomised to: usual care (UC), usual care plus the heartfailurematters.org website (HFM), and an e-health adjusted care pathway (EACP) with replacement of routine consultations by an interactive care platform with telemonitoring facilities. The participants were followed for one year. The patient's health state was measured with the EuroQol-5D-5L questionnaire at baseline, and after 3, 6, and 12 months. Data on healthcare costs were collected from hospital and general practitioner records. Analyses were conducted from the healthcare perspective. Bootstrapping was performed to assess the uncertainty surrounding the outcomes.

Results: The mean health effects in terms of quality-adjusted life years (QALYs) (range 0-1) were 0.73, 0.74, 0.76 QALY for UC, HFM, and EACP, respectively. The corresponding mean costs per patient were €5,741, €4,865, and €5,111. The net monetary benefit was positive (larger than 0) for both HFM and EACP versus usual care using a willingness to pay (WTP) of €80,000/QALY. For a WTP of up to €15,000/QALY, HFM had the highest probability of being cost-effective. At a WTP of €15,000/QALY or more, EACP had the highest probability of being cost-effective.

Conclusion: Implementing the heartfailurematters.org website in HF outpatient care results in a small increase in health effects while reducing costs. The e-health adjusted care pathway with monitoring of vital functions may provide an additional health effect at modest extra costs.

Trial registration: ClinicalTrials.gov NCT01755988

INTRODUCTION

Heart failure (HF) is a chronic progressive syndrome affecting over 23 million people worldwide. (1) It is suspected that due to ageing of the population, and improved survival after acute cardiac events, the prevalence will further increase over the next decades. (2, 3) This, along with the associated demands of adequate HF care may result in increasing costs and a shortage of resources because existing evidence-based HF management programs are time-consuming and costly. (4, 5)

Incorporation of electronic health (e-health) in HF management programs replacing routine care delivered at HF outpatient clinics to stable HF patients could reduce healthcare workers' time-investment and costs per patient. In addition, such an approach may enhance patient's well-being because of increased self-care.

Previous studies on e-health (including telemonitoring) interventions in HF evaluated such interventions on top of well-organized HF outpatient care, often resulting a poor cost-effectiveness. (6-8) In the e-Vita HF study, we evaluated the cost-effectiveness of two e-health strategies in stable HF patients managed in well-organized outpatient clinics: i) the European Society of Cardiology/Heart Failure Association (ESC/HFA) website "heartfailurematters.org (HFM website)", and ii) an interactive platform for disease management with telemonitoring facilities (e-Vita platform). (9) The HFM website was evaluated on top of usual care, and the e-Vita platform was incorporated in an adjusted care pathway replacing routine face-to-face consultations with the HF nurses.

METHODS

Study design and randomization

The e-Vita study was a parallel multicentre randomized trial with three groups. (9) In total, 450 patients were recruited from nine HF outpatient clinics in the Netherlands between October 2013 and December 2014. Participants were followed for one year. Inclusion criteria were i) a minimum age of 18 years, ii) diagnosed with HF for at least three months, iii) sufficient cognitive and physical functioning, iv) access to Internet and e-mail and basic skills to work with it (or their spouses or carers), and v) ability to read and understand Dutch. Participants were randomly allocated to one of the three groups, and written informed consent was obtained during the first study visit. Ethics approval was obtained from the Medical Ethics Committee of the University Center Utrecht, the Netherlands.

Intervention conditions

Participants allocated to group one received usual care (UC) that consisted on average of two routine consultations with the HF nurse and one with the cardiologist per year. (9) Participants allocated to group two received usual care and were instructed on how to use the heartfailurematters.org website (HFM), a practical and user-friendly website with reliable information and advices about living with HF, available in Dutch since 2012. A HF nurse provided the patients with basic guidance on its use and patients were encouraged by the HF nurse to visit the website. Additionally, participants in this group received a reminder by e-mail every three months to visit the website. Participants allocated to group three received an e-health adjusted care pathway (EACP) with the e-Vita platform for disease management replacing routine consultations with the HF nurse. The platform contained a link to the HFM website, and telemonitoring facilities to measure and store (daily) individual values of blood pressure, heart rate, and body weight. If any of the recordings of these three vital parameters were outside the predefined limits, or were not recorded, the HF nurse received an alert from the e-Vita platform. If considered necessary, the HF nurse contacted the patient by phone to ask for possible underlying reasons and HF symptoms. Furthermore, if needed, the nurse adjusted the disease management, or asked the patient to visit the outpatient clinic, or contact the general practitioner (GP), and she could suggest the GP to make a home visit, or refer the patient to the hospital. (9)

Health effects

Health effects were measured as life years and quality-adjusted life years (QALYs). Participants filled out the EuroQol-5D-5L (EQ-5D-5L) questionnaire at baseline, and after 3, 6 and 12 months. (9) This questionnaire assesses five different health dimensions: mobility, self-care, usual daily activities, pain/discomfort, and anxiety/depression. (10) The utility score of the patient's health state was calculated by using the EQ-5D-5L crosswalk index value calculator for the Netherlands. (11) The QALYs were calculated by multiplying the utility score by the time spent in that health state using linear interpolation between measurement points. (12)

Healthcare resources use and costs

Direct medical costs were used applying the healthcare perspective, and the resources directly used for the different strategies were collected (i.e. a bottom-up approach). (13) Information on hospital care was retrieved from hospital registries. The telephone contacts with the HF nurse were calculated by extrapolation (i.e. estimating a number outside the observed range) of the registration by the HF nurse during 3 weeks. Care provided by the GP, and notification of admissions in a nursing home was retrieved from the GP registries.

Collected resource use was multiplied by their respective unit costs conform the Dutch guidelines for health economic research. (14) All costs were converted to the cost level of 2014 using consumer cost indices from Statistics Netherlands. (15) GP contacts included practice visits, telephone contacts and home visits. For simplicity, we used practice visits as the unit cost for all GP contacts. The guidelines on health economic research do not provide unit costs of HF nurse's telephone contacts or home visits, or visits to the emergency department (ED) for heart care. (14) We therefore applied the cost of an emergency room visit to the heart care ED visits. (14) The unit cost of a HF outpatient clinic visit was assumed to be similar to 'any' outpatient clinic. (14) The unit cost of a HF nurse telephone contact was calculated with its average duration and the hourly wage cost of a specialized nurse. (14) The cost of a HF nurse's home visit was calculated by multiplying the specialized nurse's wage by 1.5 based on an average duration of 90 minutes per visit (including travel time).
Medication use was measured with questionnaires administered to the patient at baseline and after 12 months. Unit costs were derived from the Dutch website 'medicijnkosten.nl.' (16) Costs for maintenance of the HFM website were assumed negligible as the website is freely accessible and available worldwide. The time spent by the nurses instructing participants on its use was considered to take on average ten minutes and associated costs were based on the specialized nurses' wage. The e-health device-related costs of the adjusted care pathway were calculated including the costs for the time spent by the HF nurse to instruct, register, and monitor the participant in the EACP group. The costs of the use and maintenance of the e-health device, as well as helpdesk consultations were estimated based on the monthly costs charged in 2016 for this device to be implemented at large scale (€290 per year). Importantly, the €290 per year is an average based on monitoring HF patients with differing HF severities (i.e. NYHA I-IV). For some of these patients monitoring of vital parameters is indicated (most expensive feature of the device), for most HF patients, monitoring only answers to questionnaires is sufficient (less expensive). As we monitored vital parameters in all patients (independent of their NYHA classification), the most expensive feature of the device was used, consequently it was estimated that large scale implementation of these telemonitoring facilities would be slightly more expensive: €631 per year.

Data analyses

Missing data were imputed using multiple imputation using SPSS version 21 (Armonk, NY: IBM Corp). (17) Twenty complete data sets were created, after which these were aggregated into one dataset by taking the means.
To assess the uncertainty surrounding the life years, QALYs, and costs, bootstrapping was performed with 5,000 replications, using Excel. (12) Means and the 2.5-97.5% percentiles were used to describe life years, absolute health effects, and costs in the separate groups. As the difference in QALYs between the three strategies was expected to be small, the

Net Monetary Benefit (NMB) was calculated instead of the incremental cost-effectiveness ratios (ICER). (18) The NMB is defined as the difference in health benefits multiplied by the willingness to pay (WTP) threshold to gain one QALY, minus the difference in costs. The WTP is the amount of money policy makers are willing to pay for one additional QALY. (12) We calculated the NMB for the WTP threshold of €80,000/QALY, a threshold often used in the Netherlands for high burden diseases such as HF. (19) A positive NMB value implies that the balance between additional health effects and additional costs is favourable, whereas a negative NMB value implies this balance to be unfavourable.

An incremental cost-effectiveness plane was made including all comparisons between the three strategies to visualize the incremental QALYs and costs and their surrounding uncertainty. Cost-effectiveness acceptability curves were calculated to show the probability of the most cost-effective strategy for each given WTP.

Results on the imputed data are presented. To test the robustness of the results of the imputed data, a sensitivity analysis on data of the complete cases was performed.

RESULTS

Participants

In total, 450 participants were randomly allocated to one of the three groups, all groups included 150 patients. From all participants 80% completed all four EQ-5D-5L questionnaires (baseline, and after 3, 6, and 12 months), 64% had complete data on healthcare and medication use. In total 57% had complete data on all variables. Baseline characteristics per study group are shown in Table 1. The mean age was 66.8 (SD 11.0) years, and 74% were male. Most of them (79%) were in NYHA class I or II at baseline.

Health effects

After 12 months, 23 participants had died (4 in UC, 11 in HFM, and 8 in EACP). The mean number of life years within that year was 0.99, 0.97 and 0.97 for UC, HFM and EACP, respectively. The mean QALYs over the one-year follow-up were 0.73, 0.74, 0.76, respectively (Table 3).

Table 1. Baseline characteristics of the participants per study group

	Total (N=450)	Usual care (N=150)	Usual care + HFM website (N=150)	E-health adjusted care pathway (N=150)
Age in years, mean ± SD	66.8 ± 11.0	66.9 ± 11.6	66.7 ± 10.4	66.6 ± 11.0
Male sex, n (%)	334 (74.2)	109 (72.7)	112 (74.7)	113 (75.3)
NYHA-class, n (%)*				
I	183 (42.8)	57 (39.9)	57 (39.6)	69 (48.9)
II	154 (36.0)	55 (38.5)	53 (36.8)	46 (32.6)
III	58 (13.6)	24 (16.8)	17 (11.8)	17 (12.1)
IV	33 (7.7)	7 (4.9)	17 (11.8)	9 (6.4)
Mean duration of HF in years ± SD	3.5 ± 3.2	3.4 ± 3.0	3.8 ± 3.6	3.2 ± 2.9
Mean left ventricular ejection fraction % ± SD**	35.7 ± 10.7	36.2 ± 10.0	35.2 ± 11.1	35.9 ± 11.2

SD = standard deviation, NYHA = New York Heart Association
*Missing values: seven in usual care group, six in usual care + HFM website, nine in e-health adjusted care pathway
**Missing values: eight in usual care group, five in usual care + HFM website, five in e-health adjusted care pathway

Health resource use and costs

The mean healthcare costs per patient during one year follow-up, including device related costs, were €5,741, €4,865, and €5,111 for UC, HFM, and EACP, respectively (Table 2). After bootstrapping, the mean costs were similar with €5,734, €4,873, and €5,100 for the three groups (Table 3). The total healthcare costs over a year were mainly driven by hospitalisations, visits to outpatient clinics, medications, and 'residential care home'. In the EACP the costs per aforementioned category were in general lower, but in this group the e-health-related costs of €612 per patient per year were included.

Table 2. Mean healthcare costs with standard deviation per participant per year per treatment group

	Unit costs (€)	UC, volume in mean (SD)	UC, € (SD)	HFM, volume in mean (SD)	HFM, € (SD)	EACP, volume in mean (SD)	EACP, € (SD)
Days in hospital (general)	443*	5.3 (15.3)	2,357 ± 6,762	4.4 (11.4)	1,940 ± 5,033	3.6 (8.4)	1,601 ± 3,727
Contacts with general pratitioner†	33*	9.3 (8.0)	308 ± 263	9.3 (8.1)	304 ± 268	8.8 (7.0)	292 ± 230
Visits to HF outpatient clinic	80*	3.0 (2.2)	242 ± 179	3.1 (2.8)	250 ± 225	2.5 (2.8)	196 ± 223
Telephone contacts with HF nurse¶	3*	1.7 (7.4)	6 ± 26	0.5 (2.8)	2 ± 10	7.2 (14.1)	25 ± 48
Home visits by HF nurse¥	50*	0.0 (0.36)	2 ± 18	0.1 (1.1)	7 ± 55	0.0 (0.0)	0 ± 0
Visits to emergency room	259*	0.4 (0.90)	109 ± 233	0.3 (0.8)	90 ± 201	0.6 (2.0)	143 ± 513
Visits to emergency department for heart care	259*	0.1 (0.5)	36 ± 141	0.2 (0.6)	48 ± 157	0.1 (0.4)	29 ± 106
Visits to outpatient clinic	80*	9.6 (9.8)	768 ± 781	7.7 (7.0)	617 ± 561	7.7 (7.1)	616 ± 565
Admissions to nursing home	168*	0.0 (0.1)	306 ± 2,793	0.0 (0.1)	172 ± 1,511	0.0 (0.2)	536 ± 3,744
Admissions to residential care home	168*	0.0 (0.2)	914 ± 5,062	0.0 (0.2)	629 ± 3,859	0.0 (0.1)	332 ± 2,807
Medication	NA (various costs**)		692 ± 1,245		798 ± 1,404		729 ± 1,307
Device related costs	631***		0 ± 0		6 ± 0		612 ± 85
Total			5,741 ± 11,567		4,865 ± 8,635		5,111 ± 8,739

SD = standard deviation, HF = heart failure, UC = Usual Care group, HFM = HFM website group, EACP = E-health Adjusted Care Pathway group.
*Hakkaart-van Roijen et al, 2015
**Medicijnkosten.nl
***Care Within Reach foundation, that funded this study
†Sum of consultations at practice, telephonic consultations and home visits
¶Costs calculated by using mean duration of phone call (=6.2 minutes) times nurse's wage (=€33,32/h)
¥Costs calculated by using mean duration of home visit (=90 minutes) times nurse's wage (=€33,32/h)

Table 3. Health effects and costs outcomes per participant per year after bootstrapping and adjusted for baseline utilities

	Life years (mean, 2,5-97,5% percentile)	QALYs (mean, 2,5-97,5% percentile)	Costs (mean, 2,5-97,5% percentile)	ICER (mean, 2,5-97,5% percentile)	Net Monetary Benefit (WTP 80000)
Absolute numbers					
UC	0.99 (0.98 – 1.00)	0.73 (0.71 – 0.75)	€ 5,734 (3,985 – 7,826)	NA	
HFM	0.97 (0.94 – 0.99)	0.74 (0.72 – 0.76)	€ 4,873 (3,620 – 6,466)	NA	
EACP	0.97 (0.95 – 0.99)	0.76 (0.74 – 0.78)	€ 5,100 (3,798 – 6,651)	NA	
Incremental numbers					
HFM vs. UC	-0.02 (-0.05 – 0.00)	0.01 (-0.02 – 0.04)	€-861 (-3,347 – 1,465)	€-58,652 (-1,001,247 – 832,982) / QALY	€ 1,732 (-1,786 – 5,388)
EACP vs. UC	-0.02 (-0.04 – 0.01)	0.02 (-0.01 – 0.05)	€-634 (-3,161 – 1,714)	€-28,977 (-352,747 – 272,502) / QALY	€ 2,583 (-1,003 – 6,278)
EACP vs. HFM	-0.00 (-0.03 – 0.04)	0.01 (-0.02 – 0.04)	€ 227 (-1,814 – 2,238)	€ 22,951 (-559,192 – 626,476) / QALY	€ 971 (-2,067 – 3,851)

UC = Usual Care group, HFM = HFM website group, EACP = E-health Adjusted Care Pathway group, QALY = quality-adjusted life year, CI = 95% confidence interval, ICER = Incremental cost-effectiveness ratio, WTP = willingness to pay
Percentiles are bootstrapped
A positive NMB value implies that the balance between additional health effects and additional costs is favourable, a negative implies this balance to be unfavourable

Cost-effectiveness

For all comparisons, the NMBs were positive, implying that the balance between additional health effects and additional costs was favourable (Table 3). The incremental cost-effectiveness plane comparing HFM vs. UC, EACP vs. UC, and EACP vs. HFM is presented in Figure 1.

The cost-effectiveness acceptability curve showed that the probability of cost-effectiveness of both the HFM group and EACP group were higher than the UC group over the complete WTP range. The HFM group had the highest probability of cost-effectiveness in the WTP range of €0/QALY to €15,000/QALY. Above a WTP of €15,000/QALY, the EACP strategy had the highest probability of being cost-effective (Figure 2).

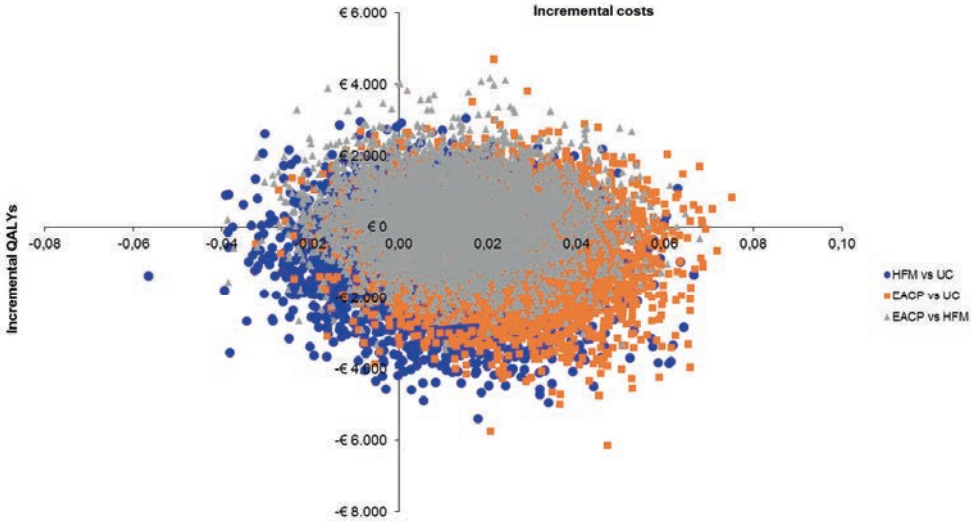

Figure 1. Incremental cost-effectiveness plane of the differences between the groups

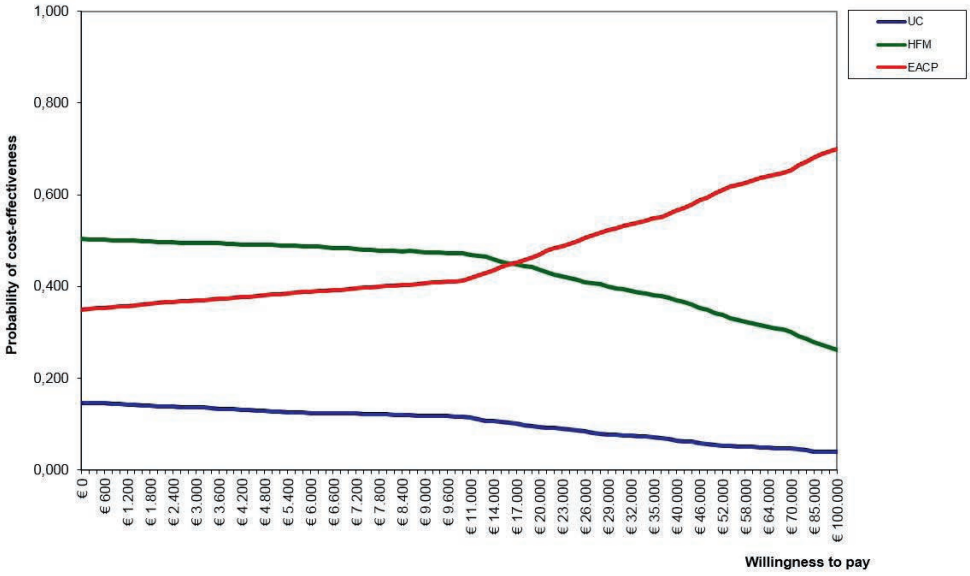

Figure 2. Cost-effectiveness acceptability curve including imputed cases

Sensitivity analyses

The mean QALYs over the one-year follow-up for the complete cases were 0.75, 0.75, 0.77, for UC, HFM and EACP, respectively, and the corresponding yearly healthcare costs were €4,489, €4,373, and €5,073. The cost-effectiveness acceptability curve showed that the probability of cost-effectiveness of the HFM group was highest in the WTP range from €0/QALY to €28,000/QALY. For a WTP higher than €28,000/QALY the EACP strategy had the highest probability of being cost-effective (Figure 3).

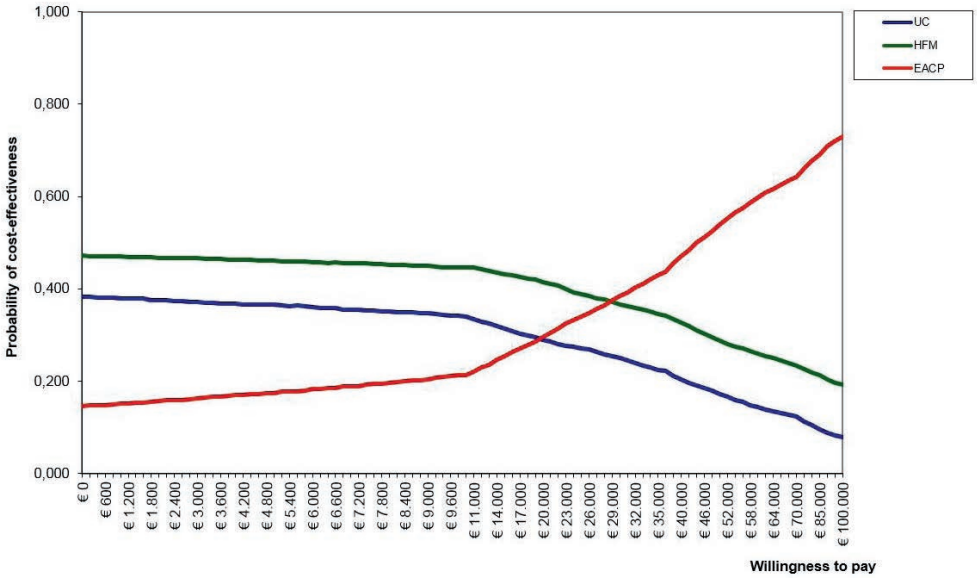

Figure 3. Cost-effectiveness acceptability curve complete cases

DISCUSSION

Main findings

Our randomized trial comparing guidance in the use of the heartfailurematters.org website (HFM) and an e-health adjusted care pathway (EACP) with usual care (UC) showed that although health effects across the three study groups were small (QALY 0.74, 0.76, and 0.73, respectively), the corresponding healthcare costs per year in stable HF patients were clearly lower for the website and e-health adjusted care pathway (€4,865, €5,111 and €5,741, respectively). This effect was driven by reduced costs of healthcare resources, mainly by fewer hospitalisation days than with the usual care strategy. The probability of cost-effectiveness of the HFM strategy was highest below a willingness to pay (WTP) €15,000/QALY, whereas above €15,000/QALY the probability of cost-effectiveness for the EACP was highest.

Comparison with literature

To the best of our knowledge, we are the first to evaluate the cost-effectiveness of an educational website. Our study is the first to quantify the effects of the heartfailurematters.org website, a site with ~1.6 million hits per year worldwide. It has been shown earlier, that educational programs can improve self-care, and that such improved self-care is associated with decreased healthcare costs. (20)

Recently, cost-effectiveness of two randomized trials on e-health replacing HF disease management face-to-face contacts have been published: the TEHAF and INTOUCH study. (8, 21)

The study population of, and usual care provided in the TEHAF study were comparable with our study; HF patients managed in Dutch HF outpatient clinics. In contrast, the TEHAF study did not show cost-effectiveness mainly because of increased costs of hospitalisation in the intervention group compared to usual care. (8) This might be explained by the items that were 'monitored' in this study; symptoms, HF knowledge, and HF-related behaviour. The HF nurse intervened when patients (i) were in high risk of symptoms, and/or (ii) had a persistent lack of knowledge or inadequate behavior (i.e. repeated inadequate answers on pre-set questions/dialogues, for example if the patient did not know that increasing weight is a risk factor (knowledge) or did not frequently weigh himself (behavior)). (22) In our study, we used an e-health tool that was as lean as possible; only body weight, blood pressure and heart rate were monitored. The HF nurse intervened when reported values were outside the individually set limits of these three vital parameters. (9) Consequently, we might presume that control of these vital parameters seem to be at least partly responsible for the reduction in hospitalisations in our study compared to UC. This interpretation is also suggested in other studies. (21, 23)

In the INTOUCH study, usual care and the study population were somewhat different. Usual care was provided in Dutch outpatient clinics, however, in addition electronic advice to the HF nurse was provided according to the ESC-HF guidelines, regarding up-titration of medication to optimal individual doses. The study population was less stable than ours as they were included when experiencing an exacerbation (i.e. needed oral or intravenous diuretics, provided during admission or at the outpatient clinic). The INTOUCH study monitored body weight, blood pressure, and if necessary heart rhythm (via an electrocardiogram). The results of these vital parameters were automatically transferred to a health monitor that generated (based on the results of these parameters) standard questions regarding the patient's health status. The answers to the questions, and the results of the vital parameters were then forwarded to the HF nurse who, if necessary, intervened. The authors performed a cost minimization analysis (i.e. only costs were compared for the different strategies). Healthcare costs were higher in the intervention group than in the control group, due to the e-health costs in the intervention arm. (21) Even though the e-health costs in our study were lower, €631 (€1,729 in the INTOUCH study), also in our study, the e-health costs were a substantial part of the healthcare costs. Reducing these costs by creating low-cost e-health technology could certainly improve cost-effectiveness of e-health interventions in HF.

Strengths and limitations

A major strength of our study is the fact that the cost-effectiveness estimates are based on data from a randomized trial. Such an approach reduces the risk of bias. In addition, the trial included 'real life' patients from different regions in the Netherlands, which increases the applicability of our findings. (24, 25) Finally, we used multiple sources for collecting cost data, from both the hospital setting and primary care.

Our study has also several limitations. In 43% of the participants, one or more variables were missing. By multiple imputation we could perform the analyses on the entire dataset, which provides better estimates than complete case analyses. (26, 27) Importantly, sensitivity analyses with complete cases yielded similar results. Our cost-effectiveness analysis was conducted from a healthcare perspective, and not a societal perspective. (28) As the majority of HF patient is aged over 70, and thus beyond the age of being productive, this will not have influenced our results. Participants allocated to usual care could also consult the HFM website as it is freely accessible. This may have reduced the contrast between usual care and the two intervention groups (HFM and EACP). To quantify this effect we asked all participants at the end of the study to report their use of the HFM website, and this was 21%, 57%, 66% for UC, HFM, and EACP, respectively. Thus, indeed some dilution may have occurred because 21% of the UC group had consulted the HFM website. This indicates that the additional effects of the HFM and EACP strategy may be somewhat underestimated, and therefore their costs overestimated in our study.

Implications and conclusion

As the HFM website is cost-effective (at a WTP <20,000/QALY) and freely accessible, more explicit implementation in routine outpatient care of HF patients should be considered. Our EACP group showed a remarkable reduction in use of healthcare recourses compared to usual care. With reduction in e-health costs, for example by using already available and widespread smart phones applications cost-effectiveness of HF care may further improve.

We conclude that implementing the heartfailurematters.org website in the HF usual outpatient care results in a small increase in health effects while reducing costs. The e-health adjusted care pathway, with replacement of routine HF-management program consultations and including monitoring of vital functions may provide additional health benefits at modest extra costs.

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7

Representativeness of participants in heart failure e-health trials: a report from the e-Vita HF study

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RESEARCH LETTER

E-health is rapidly emerging in heart failure (HF) management. E-health trials evaluate health services and information delivered through internet and related technologies such as telemonitoring systems. (1, 2)

Randomized controlled trials (RCTs) provide the strongest evidence on the effects of interventions. However, eligibility criteria and the willingness to participate may result in differences between participants and nonparticipants. As a consequence, the results of the trial may not be generalizable to the whole domain of patients. (3)

Selectivity of participants in HF RCTs is well-known (4), but is not yet investigated in HF e-health trials. Better insight in representativeness of patients in e-health RCTs is pivotal. HF e-health trials may be even more sensitive to selectivity then HF device and drug trials, as they require more active participation and technical "savviness". We aimed to compare the characteristics of participants with nonparticipants in the e-Vita HF study, a 3-arm RCT on the effectiveness of two e-health tools in patients with HF; (i) the European Society of Cardiology/Heart Failure Association website heartfailurematters.org and (ii) an interactive platform for HF disease management, including telemonitoring facilities, and with a link to heartfailurematters.org were compared with (iii) usual care as delivered by 9 HF outpatient clinics in the Netherlands. (5) We additionally compared the characteristics of e-Vita HF participants with the population of previously published randomized HF e-health studies summarized in a recently published Cochrane review. (6)

Important eligibility criteria for the e-Vita HF study were (i) confirmed HF for at least 3 months and (ii) access to internet, e-mail and basic user skills. In total, 405 HF patients consented to participate in this sub-study, that is, participants from 8 of the 9 HF outpatient clinics included in the e-Vita HF trial. (5) A random sample of nonparticipants (n=402) from the participating outpatient clinics in this sub-study was taken as the comparison group. Demographic and disease-specific characteristics of the participants and nonparticipants were collected at baseline. As a surrogate to the individual's socio-economic status (SES), we used the area SES by linking the 4 digits of the Dutch postal codes to the SES levels of the Netherlands Institute for Social research database. (7) This SES was categorized as low if <0, middle if 0, and as high if SES was >0. Participants signed an informed consent. Available data of the nonparticipants were analyzed anonymously, as was approved by the Medical Ethical Committee of the University Medical Center Utrecht, the Netherlands.

Table 1 shows the characteristics of participants and nonparticipants in the e-Vita HF study. Participants were younger (mean age 66.7 vs 73.4 years, p< .001), more often male (75% vs 58%, p< .001), and had in general fewer comorbidities. After adjustment for age, anemia, and angina pectoris were no longer significantly less prevalent in participants compared to nonparticipants, whereas SES now was significantly higher in participants compared to nonparticipants.

Table 1. Characteristics of participants and nonparticipants in the e-health e-Vita HF trial

	Participants (N=405)	**Nonparticipants (N=402)**		
Demographics	%	%	P value*	Adjusted P value†
Female	25.2	42.3	**<.001**	**<.001**
Mean age in y (SD)	66.7 (10.8)	73.4 (11.1)	**<.001**	NA
SES‡				
Low	16.5	19.9	.34	**.02**
Middle	38.0	39.3		
High	44.9	40.8		
Comorbidities				
Angina pectoris	17.8	24.6	**.02**	.15
Prior MI	42.2	41.0	.73	.42
Hypertension	44.0	62.2	**<.001**	**<.001**
Hyperlipidemia	40.0	38.3	.62	.57
Anemia	15.1	20.9	**.03**	.79
Diabetes	25.2	30.1	.12	.25
Renal insufficiency§	15.6	40.3	**<.001**	**<.001**
COPD or asthma	25.7	21.4	.15	.07
Cancer	18.0	21.4	.23	.62
Sleep disorders	9.6	8.7	.65	.70

COPD, chronic obstruct pulmonary disease; MI, myocardial infarction; SD, standard deviation; SES=socio-economic status.
*P-value calculated with chi-square test and *t* tests.
†P-value calculated with multiple (ordinal) logistic regression analysis with adjustment for age.
‡0.5% missing among participants.
§Renal insufficiency = patients < 65 y, creatinine clearance < 45 ml/min/1,73m2; ≥ 65 y, creatinine clearance < 30 ml/min/1,73m2.

In the Cochrane review, we identified 18 telemonitoring studies, published between 2001 and 2014 (data on nonparticipants was not presented). The mean age of participants was 68 years (range 54 to 78 years), 73% (range 35 to 85%) were men, 30% (4 to 43%) had diabetes and 43% (15 to 67%) was known with hypertension. These characteristics were similar to participants of the e-Vita HF trial.

Our study is the first to evaluate the representativeness of participants in an HF e-health RCT. As in RCTs evaluating pharmaceutical interventions in chronic HF patients, participants in the e-Vita HF study were younger, more often male, and with fewer comorbidities than nonparticipants. (4)

The SES of participants was higher than of nonparticipants in our e-Vita HF trial after adjustment for age. This finding is in line with previous studies that showed an association between the level of SES and the use of internet in elderly. (8, 9)

Results of the e-Vita HF trial show that patients willing to participate are younger, more often male, wealthier and healthier than those who decline to participate. This implies that clinicians should realize that results from HF e-health trials constrain to this population, but also that e-health tools should be made better accessible to the most vulnerable of the HF patients.

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8

General discussion

Heart failure (HF) is a chronic progressive syndrome characterized by the heart's inability to pump enough blood to meet the body's needs. (1) Currently, approximately 23 million people are affected worldwide. (2, 3) This number is expected to rise because of aging of the population. (4)

HF largely affects the health status of patients, and has a large impact on the healthcare budget (i.e. 1 to 2%). (5, 6) Drug therapy and devices are available that can improve prognosis in HF patients. In addition, disease management programs have been developed for HF patients targeting self-care, education on HF, lifestyle, adherence to therapy, and monitoring of vital functions (such as blood pressure, heart rate, and body weight). (7) Although effective, such programs are resource demanding, and allow only relatively few patients to be managed per healthcare worker. Given the constraints on healthcare expenditure, especially in view of the increasing number of older adults, nearly all western countries are in need for more efficient HF management capable of serving more patients per healthcare worker. One solution is to replace parts of disease management programs by e-health. This seems certainly feasible in stable HF patients who are sufficiently educated on HF and adequately up titrated with evidence-based HF drugs. (8) An additional benefit of e-health may be the enhancement of autonomy and self-care of the patient, which may help to prevent unplanned hospital admissions. (9)

Previous studies that assessed the effect of e-health tools in HF reported inconsistent results, (10, 11) and most did not apply e-health as replacement, but on top of usual care. To be efficient, substitution of usual care by e-health seems more logical, but the effects of such a strategy are currently unknown. (12) Importantly, previous studies did not measure the effect on self-care, while self-care is – be it a challenging concept to measure and interpret – a 'natural' endpoint for e-health interventions targeted at behavioural change.

In this thesis, we addressed the following questions:

- What is the worldwide uptake of the freely accessible ESC/HFA website heartfailurematters.org, an e-health tool providing information on HF to patients and carers?
- What can be considered as a clinically relevant threshold in patient reported self-care outcomes in HF?
- What is the effect of an e-health adjusted care pathway (replacing routine consultations) on self-care, health status, hospitalisations and mortality in stable HF patients?
- What is the effect of the ESC/HFA website heartfailurematters.org on self-care, health status, hospitalisations and mortality in stable HF patients when added to care as usual provided by the HF outpatient clinic?
- What is the short-term cost-effectiveness of the website heartfailurematters.org, and an e-health adjusted care pathway (replacing routine consultations)?
- Do participants in HF e-health trials differ from the HF population at large?

Main findings of this thesis

- The freely accessible e-health tool, the www.heartfailurematters.org (HFM website), a website with HF information for HF patients and their carers was launched in 2007. Initially in English, but shortly afterwards followed by other languages, i.e. French, Spanish, German, Russian, Dutch, Greek, Arabic, and Portuguese. The website has increasingly been visited over the years. Most users (72-75%) found the site by using a search engine. Increasingly, desktops and smartphones were used to visit the website; 50% by desktop, and 38% by smartphone in 2015. Nevertheless, it certainly has not yet reached its full potential; less than 2 million users visited the website in 2015 while worldwide an estimated 23 million people is affected by HF. (2)

- Patient reported self-care outcomes in HF are often measured by the European Heart Failure Self-care and Behaviour (EHFScB) scale. Among participants in the COACH trial (conducted from 2002 to 2007 in the Netherlands) (13), we looked at the distribution of the EHFScBs scores as it provides information on whether for example the population and its subgroups have a low or a high score on average. The EHFScB scores were similarly normally distributed among the study population and its clinically relevant subgroups (e.g. age (<60, between 60 and 80, ≥80 yrs), gender (female, male), marital status (having a partner, single)), with a mean between 57.8 (SD 19.4) and 72.0 (SD 18.0).

A single threshold of 70 accurately discriminates between patients with adequate and inadequate self-care. In participants with a score of 70 or more significantly lower all-cause hospitalisations occurred than in the remaining 559 patients with inadequate self-care (less than 70 on EHFScB scale).

- Both the HFM website and an e-health adjusted care pathway showed a significant improvement in self-care at 3 months compared to usual care; the mean EHFScB scale score was 73.5 vs. 70.8 (95%CI 0.6- 6.2), and 78.2 vs. 70.8 (95%CI 3.8 – 9.4) respectively. After one year, however, self-care no longer differed between the groups (mean 72.1 vs. 72.7 (website vs. usual care) and 76.1 vs. 72.7 (adjusted care pathway vs. usual care). Importantly, patients with HF were equally satisfied with the e-health adjusted care pathway (without having routine consultations with the HF nurse) as with usual care as measured on a Visual Analogue Scale (0 = no satisfaction, 100 = maximal satisfaction); 71.7 vs. 75.3.

- Implementing the heartfailurematters.org website in the HF outpatient care (usual care in our study) resulted in a small improvement in quality-adjusted life years (QALYs) while the costs were reduced compared to care as usual.

The e-health adjusted care pathway with monitoring of vital functions and replacing routine contacts may provide an additional QALY, at small costs.

- Patients willing to participate in the e-Vita HF trial were younger, more often male, wealthier, and healthier than those who declined to participate. Healthcare workers interpreting our results and applying the intervention in daily practice should bare this in mind. Also the

results of other studies on e-health in HF patients should be interpreted with caution, as selective inclusion was similar in earlier e-health HF trials.

In light of our main findings, three aspects of e-health in HF care need special attention in order to further improve HF care and its efficiency.
- How to sustain the short-term effect of e-health tools?
- The need to evaluate and update freely accessible medical websites
- Are we ready to replace face-to-face contacts by e-health interventions in stable HF patients?

How to sustain the short-term effect of e-health tools?
In the e-Vita HF trial a short-term effect was observed, but the long-term effect on self-care of the e-health interventions was disappointing. With a long-term beneficial effect on self-care, also a beneficial effect on health status, hospitalisations, and mortality may be achieved. (9)
To establish a long-term beneficial effect of e-health interventions on self-care behaviour, maintenance of change in a patient's behaviour is essential.
By trying to explain our lack of a long-term effect, we studied the literature regarding effective components of e-health interventions on maintaining behavioural change. We found the following potentially useful 'tools' to ensure long-term effects.
1) Behavioural change may be achieved by a pro-active approach; for example, the e-health tool can initiate trigger and push messages including health information or feedback to patients. (14) Continuing personalised stimulation may thus be delivered.
2) Multiple (5 or more) behaviour change techniques (i.e. strategies used in an intervention to promote behavioural change such as problem solving, goal setting and self-monitoring) could be applied at one time. Multiple, instead of a single item tends to induce larger and sustainable effects on behaviour. (15, 16)
In the e-Vita HF study the pro-active approach and multiple behaviour change techniques were incorporated in the intervention: a pro-active approach by providing extra information about the e-health tool through e-mails, and multiple behaviour change techniques included self-monitoring, providing feedback on performance, barrier identification/problem solving, providing instruction, and environmental restructuring. Thus, the question remains why did, despite the use of these 'tools', our study not show a long-term effect.
3) Daily pre-set dialogues and questions about their HF symptoms, HF knowledge, and HF related behaviour may be important to achieve maintenance of behavioural change. Another study evaluating e-health against usual care in stable HF patient managed in outpatient clinics in the Netherlands (TEHAF study), showed a long-term effect on self-care. E-health compared to usual care significantly improved self-care after 3 months [mean difference -1.6 (p-value 0.004)] and after 12 months [mean difference-2.2 (p-value <0.001)]. Possibly, the daily pre-set dialogues and questions about their HF symptoms, HF knowledge, and HF related behaviour

in the e-health group played a role. Patients had to answer questions via the telemonitoring system, with a HF nurse intervening when patients (i) reported an increase in symptoms indicative of volume overload, and/or (ii) had a persistent lack of knowledge or behaviour (i.e. repeated inadequate answers on pre-set questions/dialogues, for example if the patient did not know that increasing weight is a risk factor (knowledge) or did not frequently weigh himself (behaviour)). (17) In our study, the e-health tool was as lean as possible, only body weight, blood pressure and heart rate were monitored, and the HF nurse intervened when reported values were outside the individually set limits of these three vital parameters. (17) Possibly inclusion of daily pre-set dialogues and questions (as applied in the TEHAF study) in our study, could have helped to achieve long-term effects of the e-health intervention we evaluated.

4) Incorporation of the Theory of Planned Behaviour (TPB) to target the behaviour of interest (in this case self-care) seems useful to achieve a long-term effect. (18) In the TPB model intention is the key factor and is assumed to capture the motivational factors that influence behaviour. Intention is influenced by three determinants: attitudes towards behaviour (i.e. appraisal of the behaviour in question), subjective norm (i.e. perceived social pressure) and perceived behavioural control (i.e. perception of the ease or difficulty based on available resources and opportunities of performing the behaviour of interest, is also assumed to reflect past experience as well as anticipated impediments and obstacles). The general rule is that the more favourable the attitude and the subjective norm with respect to the behaviour is and the greater the perceived behavioural control, the stronger an individual's intention to perform the behaviour under consideration, and this will most probably result in the behaviour of interest. (19)

Revisiting the characteristics of the e-Vita HF intervention to see if all the three determinants of the TPB are sufficiently addressed learns that only a few characteristics (i.e. the HF nurse discussing barriers of performing the requested life styles when the vital parameters are outside the limits) address attitudes towards behaviour, subjective norm and perceived behavioural control. Adding parts of motivational interviewing (i.e. assessing a patient's readiness and developing strategies to move towards taking action to change behaviour) at different time points within the intervention could address these issues, (9) change behaviour, maintain change, and thereby prolong the effect of the intervention. TPB has shown to improve the effectiveness of internet interventions on health related behaviour change in for example people with diabetes mellitus (15) but are rarely used in e-health tools. (16)

The need to evaluate and update freely accessible medical websites

The number of freely accessible websites with medical information for patients and their carers is large and increasing rapidly. In the Netherlands, several websites with credible and independent information about symptoms, diseases, health, and drugs are very popular.

Thuisarts.nl (thuisarts can be translated as “home doctor”) is a website focusing on how patients can deal with common complaints, such a cough or sore throat. Apotheek.nl is a website with detailed information on existing drugs such as the pain killer ‘diclofenac’. Maintenance and keeping these websites up to date is the responsibility of the Dutch General Practitioner College (NHG) and pharmacist organization (KPMG), respectively. These websites were initially designed to supplement the consultation between patients and general practitioner, and pharmacist. However, they also reduce the workload of healthcare professionals enormously, probably because they inform the patient in such a way that they can solve their health problems without seeking support from their treating physician or pharmacist. (20, 21) To keep the information and features (i.e. according to modern technological standards and user preferences) on the website up to date, timely and adequate maintenance is vital. (20) However, it demands considerable time of content experts and IT support. If not maintained properly, ‘bugs’ appear, and these can reduce visits to the website.

To the best of our knowledge we were the first to formally evaluate the uptake of a HF information website (chapter 2). Previous studies evaluating websites with HF information have only evaluated the websites in a small sample of patients who were followed closely, and were encouraged to use the website. This may have resulted in overoptimistic ‘compliant use’. (22-24) For several other diseases, however, the ‘real life’ uptake of some publicly available information websites has been evaluated using similar methods, such as Google Analytics (GA), as applied in our study. Analyses of a Dutch information website on ‘nutrition and cancer’, and a Dutch website for lung cancer, (25, 26) showed that the use of the websites increased during the study period, which is in line with our results evaluating the HFM website. (25, 26) The ‘nutrition and cancer’ website was visited 109,596 times in a one year study period. (26) This is around four times higher than the number of sessions on the Dutch HFM website. Importantly, however, the ‘nutrition and cancer’ website was a national initiative and intensively promoted (e.g. all outpatient clinics in the Netherlands received posters and folders to hand out to patients), while the Dutch version of the HFM website was launched in 2012 and not actively promoted on a national level during the conduct of the e-Vita-HF study. This was decided, to keep the risk of dilution of contrast between usual care and the two intervention groups to a minimum.

Uptake of websites can easily be evaluated with GA. GA provides insight in ‘what’ the user is doing. The users’ behaviour can reveal necessary changes of the website. It offers, however, no insight into the motivation or decision process of the user. (27, 28). For the latter, user satisfaction techniques can be used such as interviews, expert opinions, and ‘think aloud’ (by asking users/cares/patients to verbalize their thoughts as they move through the website). (29, 30)

With the increasing interest of lay people in medical information websites, regular evaluation of such websites is vital to assess whether their aims are met. In this era of rapid ICT developments, the extent to which these goals are reached can rapidly change when newer, more user friendly competing (maybe even less credible) sites are launched.
Measuring a website's effect might be difficult as it requires to follow a group of users for a certain period of time, and these users should be representative for website users. However, it is certainly worthwhile when lots of efforts, time and money is put in updating the content and maintenance of a website. Most existing medical sites are not regularly evaluated. This is unfortunate, since this is likely to improve the sites' credibility and impact.
'Credible' medical websites, such as the websites thuisarts.nl mentioned earlier, in general update their content continuously. This takes a lot of time and effort. However, it remains challenging for users to distinguish credible sites from those not trustworthy. (31) The Health on the Net Foundation (HON) Code of Conduct (HONcode) certification evaluates medical websites free of charge and provides certification with regard to the following eight principles: authority, complementarity, privacy, attribution, justifiability, transparency, financial disclosure, advertising policy. (32) If the site satisfies, a certificate is provided, including a digital stamp on the respective website for one year. The presence of the HONcode certification can also be assessed via www.healthonnet.org. To increase the influence of credible and freely accessible medical websites, it is important to communicate to the (potential) users that the information can be trusted. In addition, campaigns to inform the public on how to recognize credible medical websites are essential. Moreover, efforts to improve the ranking of these website in search engines (such as Google) is important.

Are we ready to replace face-to-face contacts by e-health interventions in stable HF patients?

E-health has not often been evaluated as a replacement of (a part of) conventional disease management programs, while this is considered a relevant approach to assess e-health' full potential in an era with increasing demand on healthcare workers and healthcare budgets. (12)
Two other Dutch studies, recently published, incorporated replacement of face-to-face consultations by telemonitoring; the TEHAF and the INTOUCH study. (33, 34) In the TEHAF study, half of the routine consultations (4 per year) with the HF nurses of the outpatient clinic was replaced by e-health. In the INTOUCH study, all routine consultations were replaced. The results of the INTOUCH study are difficult to interpret because of a low number of participants (83 usual care and 94 telemonitoring with replacement of routine consultations). (33) Both studies conclude that it seems safe to replace routine consultations by telemonitoring. This is a somewhat unexpected conclusion, as the aim of both studies was to show superiority of the e-health intervention on patient-outcomes, and thus the power of these studies to show

that e-health does not increase the incidence of effects, such as mortality or hospitalisations, is too limited. When assessing whether a new intervention is 'not worse' than usual care, a non-inferiority design is required, including a non-inferiority margin within which the effect estimate of the safety outcome (e.g. mortality) is considered to be equally effective as usual care. (35) This typically requires the inclusion of large number of participants. Neither these two earlier studies, nor the e-Vita HF trial applied a non-inferiority design and an acceptable non-inferiority margin for relevant safety outcomes such as mortality. Therefore we cannot conclude that the e-health intervention is as safe as the care as usual with more routine face-to-face contacts. We can only conclude that in none of these three studies a clear safety concern was identified. To prove safety, a large non-inferiority trial is needed. (36) Aggregating the individual patient data of available studies and performing an IPD meta-analysis might be an alternative to increase power and assess safety. (37)

Recommendation for future research and concluding remarks

- To establish long-term effects of e-health tools that target behavioural change (such as self-care) it may be helpful to more explicitly integrate suitable behavioural models in the developmental phase of the intervention. Furthermore, providing pro-active messages (e.g. triggers, push-messages) should be considered. Finally, given the fact that ICT is rapidly evolving, the evaluation of an e-health tool as a dynamic intervention (i.e. the intervention may be adjusted during evaluation) should be considered as it better reflects the real world of e-health. This could be achieved by applying adaptive trial designs. (38)
- It is recommended that freely accessible medical information websites should formally be evaluated on a regular basis to ensure that the websites' goals are reached and that this remains the case in an era of rapid ICT developments. Also, to improve HF care with freely accessible medical websites it is important to be transparent in the credibility of the sites, e.g. by showing certification outcomes by an organization such as HONcode. In addition, campaigns to inform the public on how to recognize credible medical websites and efforts to improve the ranking of these website in search engines (such as Google) are important.
- Patient reported outcomes (PROs), e.g. the EHFScB scale we used as the primary outcome in our study, are important for evaluating the effect of e-health interventions, and are receiving more attention as possible outcome parameters in trials. (39) Before such parameters can be included as the primary outcome in trials, the interpretability of a PRO should be known. Otherwise it is difficult to establish whether observed differences between study groups are clinically relevant. (40) Nevertheless, until now, studies on the interpretability of PROs used in medical research are very scarce. Studies, as the one we performed on the EHFScB scale, aimed at improving the interpretability of HF PROs are urgently needed.

Conclusions

The short-term effect of e-health tools in HF patients might be prolonged by integrating a behavioural model and a clear pro-active approach including tailored push messages.

To decide on replacement of face-to-face care by e-health, further research on safety is needed. The more because such an intervention seems cost-effective.

It is important to evaluate freely accessible medical websites and officially communicate their credibility to patients and their carers.

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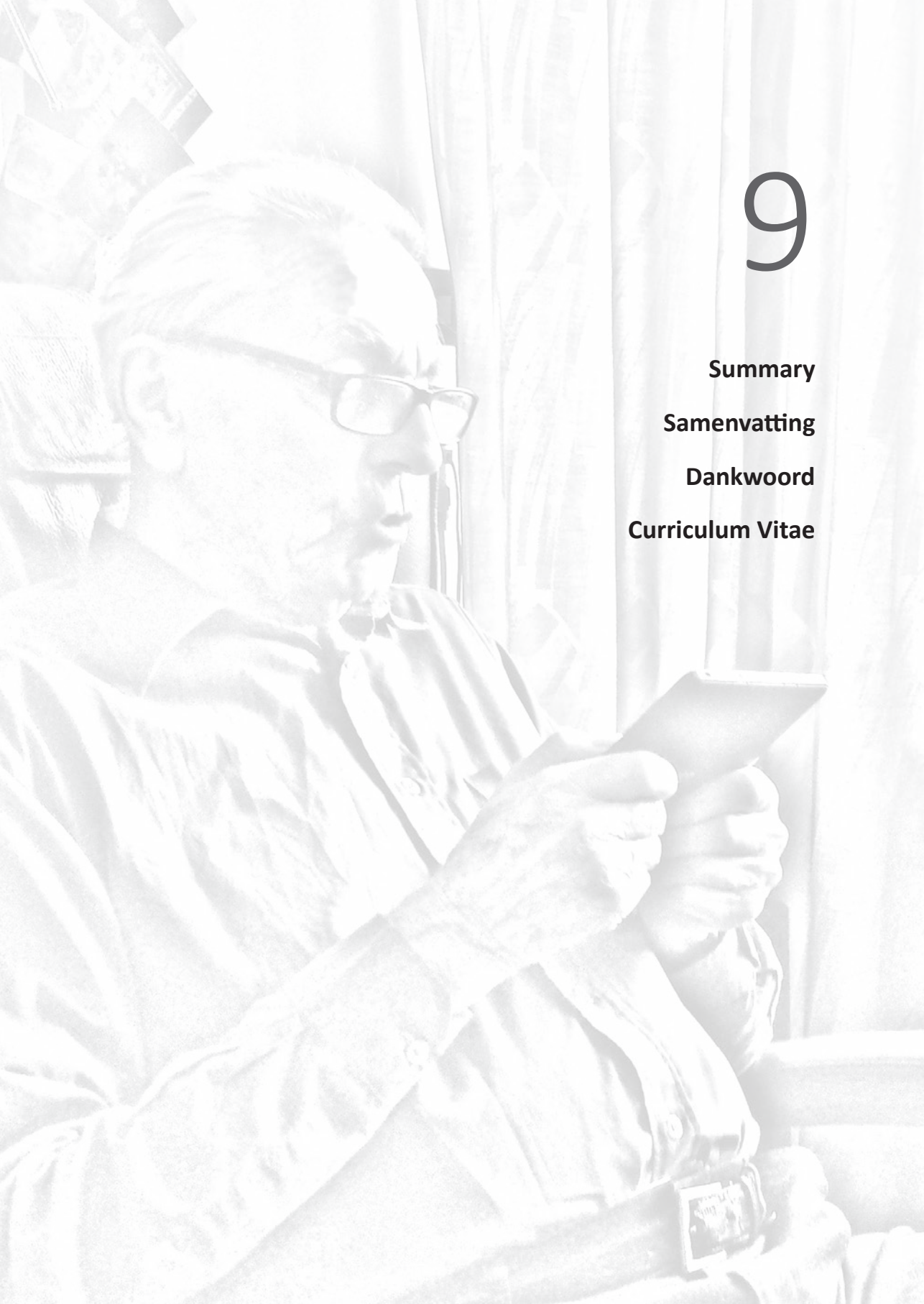

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Summary

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Summary

Chapter 1 describes the rationale of the studies in this thesis. Heart failure (HF) is a chronic progressive syndrome due to the inability of the heart to pump enough blood to meet the body's needs. Approximately 23 million people are affected worldwide. This number is expected to rise because of aging of the population.
HF has a major impact on the health status of the patients, and the healthcare budget. Widely implemented drug therapy and devices can improve prognosis in HF patients. Also, disease management programs are available targeting self-care, knowledge on HF, lifestyle, adherence to therapy, and monitoring of vital functions (such as blood pressure, heart rate, and body weight). Although effective, such programs allow relatively few patients to be managed per healthcare worker as these are resource demanding. Given the constraints on healthcare budget, especially in view of the increasing number of older adults, there is an international need for more efficient HF management capable of serving more patients per healthcare worker. One solution is to replace parts of disease management programs by e-health. This seems certainly feasible in stable HF patients (i.e. sufficiently educated on HF and adequately up titrated with HF drugs). In addition, e-health may enhance autonomy and self-care of the patient, and that may help to prevent unplanned hospital admissions.
Previous studies that assessed the effect of e-health tools in HF reported inconsistent results, and most did not apply e-health as replacement, but on top of usual care. Effects of replacement of usual care by e-health are currently unknown. Also, previous studies did not measure the effect on self-care, while self-care is – although a challenging concept to measure and interpret – a 'natural' endpoint for e-health interventions targeted at behavioural change.
The main aim of this thesis was to study the effect and the cost-effectiveness of two e-health interventions, of which one included replacement of usual care by e-health, on self-care in HF patients by conducting the e-Vita HF study. In addition, we describe the worldwide use of one of the e-health tools used in the interventions. Finally, we provide information on how to interpret the self-care results of the study and elaborate on the generalizability of the results.
In **chapter 2** we describe the background, objectives, worldwide use, lessons learned and future directions of one of the e-health tools evaluated in the e-Vita HF study: the 'heartfailurematters.org' website (HFM website), a website with reliable information on HF. In 2007, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) launched this information website for patients, their carers, health care professionals, and the general public to provide a practical tool with advice and guidelines on living with HF on a worldwide level. The website is now available in 9 languages. The number of sessions as measured by Google analytics was used to explore the use of the HFM website from 2010 to 2016.

Worldwide, the annual number of sessions increased from 416,345 in 2010 to 1,636,368 in 2015. Most users (72-75%) found the site by using a search engine. Desktops and more recently also smartphones were used to visit the website; in 2015 by 50% and 38% respectively. Although, increasingly used, the HFM website has not reached its full potential yet: less than 2 million users are visiting the website in contrast to an estimated 23 million people with HF worldwide. The uptake and use could be further improved by a continuous process of qualitative assessment of users' preferences, professional helpdesk facilities, and comprehensive information technology and promotional support.

In **chapter 3**, we report on our assessment of the interpretability of the European Heart Failure Self-care behaviour scale (EHFScBs) score, a valid patient-reported questionnaire to measure self-care behaviour of HF patients. Among 1,023 participants in the COACH trial (conducted from 2002 to 2007 in the Netherlands), we looked at the distribution of the EHFScBs scores as it provides information on whether for example the population and its subgroups have a low or a high score on average. The EHFScB scores were similarly normally distributed among the study population and its clinically relevant subgroups (e.g. age (<60, between 60 and 80, ≥80 yrs), gender (female, male), marital status (having a partner, single)), with a mean between 57.8 (SD 19.4) and 72.0 (SD 18.0).

A single threshold of 70 accurately discriminated between patients with adequate and inadequate self-care. In participants with a score of 70 or more significantly lower all-cause hospitalisations occurred than in the remaining 559 patients with inadequate self-care (less than 70 on EHFScB scale).

In **chapter 4,** the rationale, design, study population, power calculation, patient recruitment, interventions, outcome measures and statistical analysis of the e-Vita HF study are described (i.e. study protocol).

In the e-Vita HF study we aimed to assess the effect on self-care of (1) the ESC/HFA website heartfailurematters.org on top of usual care, and (2) an e-health adjusted care pathway with replacement of routine HF nurse consultations in stable HF patients. Finally, we aimed to evaluate the cost-effectiveness of these interventions. A three-arm parallel randomized trial was conducted. Group 1 received usual care; group 2 usual care plus the HFM website; and group 3 got the adjusted care pathway with an interactive platform for disease management (e-Vita platform), including a link to the HFM website and telemonitoring facilities, which replaced routine consultations with HF nurses at the outpatient clinic. We planned to include 414 patients from 10 Dutch HF outpatient clinics or general practices and to follow them for 12 months. Patients were included if they have had an confirmed diagnosis of HF for at least 3 months, and access to internet, e-mail and basic user skills. The primary outcome was self-care as measured by the EHFScB scale. Secondary outcomes were quality of life, cardiovascular- and HF-related mortality, hospitalisation, and its duration as captured by hospital and general practitioner registries, use of and user satisfaction with the HFM website, and cost-effectiveness.

Chapter 5 presents the results of the e-Vita HF study.
In total, 450 (150 per group) patients were included in the trial. The mean age was 66.8 (SD 11.0) years, 74.2% were male, and 78.8% classified as NYHA I or II at baseline. After 3 months follow-up, the mean score on the self-care scale was significantly higher in the groups using the website and the adjusted care pathway compared to usual care: 73.5 vs. 70.8 (difference 2.7, 95%CI 0.6 – 6.2), and 78.2 vs. 70.8 (difference 7.4, 95%CI 3.8 – 9.4), respectively. The effect weakened during the following 9 months until no differences after one year between the groups (difference -0.6, 95%CI -3.7 – 3.4, and 3.4 95%CI -0.7 – 6.4, respectively). Quality of life and HF knowledge revealed the same pattern as was observed in self-care. Other secondary outcomes did not clearly differ between the groups.
In **chapter 6**, we report the cost-effectiveness of the e-Vita HF trial.
The patient's health state was measured with the EuroQol-5D-5L questionnaire at baseline, and after 3, 6, and 12 months. Data on healthcare costs were collected from hospital and general practitioner records. Analyses were conducted from the healthcare perspective. We performed bootstrapping to assess the uncertainty surrounding the outcomes.
The analysis showed that the mean health effects in terms of quality-adjusted life years (QALYs) (range 0-1) were 0.73, 0.74, 0.76 QALY for the usual care, website, and e-health adjusted care pathway group, respectively. The corresponding mean costs per patient were €5,741, €4,865, and €5,111. The net monetary benefit was positive (larger than 0) for both the website and e-health adjusted care pathway group versus the usual care group using a willingness to pay (WTP) of €80,000/QALY. For a WTP of up to €15,000/QALY, the website group had the highest probability of being cost-effective. At a WTP of €15,000/QALY or more, the e-health adjusted care pathway had the highest probability of being cost-effective.
Thus, implementing the heartfailurematters.org website in HF outpatient care results in a small increase in health effects while reducing costs. The e-health adjusted care pathway with monitoring of vital functions may provide an additional health effect at modest extra costs.
In **chapter 7**, we describe the representativeness of patients in e-health RCTs.
Therefore, we compared the characteristics of participants with nonparticipants in the e-Vita HF study. We also compared the characteristics of e-Vita HF participants with the population of previously published randomized HF e-health studies summarized in a recently published Cochrane review.
Of the e-Vita HF participants a random sample of 405 HF patients consented to participate. A random sample of nonparticipants (n=402) was taken as the comparison group. Demographic and disease-specific characteristics of the participants and nonparticipants were collected at baseline.
Participants were younger (mean age 66.7 vs 73.4 years, p< .001), more often male (75% vs. 58%, p< .001), and had in general fewer comorbidities. After adjustment for age, anaemia, and angina pectoris were no longer significantly less prevalent in participants compared

to nonparticipants, whereas SES now was significantly higher in participants compared to nonparticipants.
In the Cochrane review the mean age of participants was 68 years (range 54 to 78 years), 73% (range 35 to 85%) were men, 30% (4 to 43%) had diabetes and 43% (15 to 67%) was known with hypertension. These characteristics were similar to participants of the e-Vita HF trial.
In **chapter 8**, the general discussion, we summarize the main findings of this thesis. In addition, we elaborate on three aspects of e-health in HF care that need special attention to further improve HF care and its efficiency. First, we discussed how to sustain the short-term effect of e-health tools, or better how to maintain a change in self-care behaviour with e-health interventions. Based on literature, possibly daily pre-set dialogues and questions about HF symptoms, knowledge, and related behaviour may be important to achieve maintenance of behavioural change. Also, incorporation of the Theory of Planned Behaviour (TPB) to target the behaviour of interest (in this case self-care) seems useful to achieve a long-term effect.
Second, we discussed the need to evaluate and update freely accessible medical websites.
In the Netherlands, several websites with credible and independent information about symptoms, diseases, health, and drugs are very popular. For example, Thuisarts.nl (thuisarts can be translated as “home doctor”) is a website focusing on how patients can deal with common complaints, such a cough or sore throat. These websites reduce the workload of healthcare professionals enormously. With the increasing interest of lay people in medical information websites, regular evaluation of such websites is vital to assess whether their aims are met, especially when lots of time, efforts, and money is put in updating the content and maintenance of that site. In this era of rapid ICT developments user friendliness of websites is evolving fast. Thus the extent to which the aims of a website are met can rapidly change when newer, more user friendly competing (maybe even less credible) sites are launched.
Most existing medical sites are not regularly evaluated. This is unfortunate, since this is likely to improve the sites’ credibility and impact. To increase the influence of credible and freely accessible medical websites, it is also important to communicate to the (potential) users that the information can be trusted, for example by displaying a certificate from a trustworthy certifying organization (such as the Health on the Net (HON)).
Finally, we discussed if we are ready to replace face-to-face contacts by e-health interventions in stable HF patients. At this point, we cannot conclude that the e-health intervention is as safe as the care as usual with more routine face-to-face contacts. We can only conclude that in none of the previously conducted relevant studies (i.e. e-Vita HF, INTOUCH and TEHAF) a clear safety concern was identified. However, to prove safety, a large non-inferiority trial is needed. Aggregating the individual patient data of available studies and performing an IPD meta-analysis might be an alternative to increase power and assess safety.
To conclude, the short-term effect of e-health tools in HF patients might be prolonged by integrating a behavioural model and a clear pro-active approach including tailored push

messages. Also, it is important to evaluate freely accessible medical websites and officially communicate their credibility to patients and their carers.
To decide on replacement of face-to-face care by e-health, further research on safety is needed. This is worthwhile because such an intervention seems cost-effective.

Samenvatting

Hoofdstuk 1 bevat de rationale van de studies in dit proefschrift. Hartfalen (HF) is een chronisch progressief syndroom veroorzaakt door het onvermogen van het hart om voldoende bloed rond te pompen door het lichaam. Wereldwijd lijden ongeveer 23 miljoen mensen aan HF. Verwacht wordt dat dit aantal zal toenemen door de vergrijzing van de bevolking.
HF heeft een grote invloed op het welbevinden van patiënten en het gezondheidszorg budget. Medicamenteuze behandeling en apparaten (zoals interne defibrillatoren) kunnen de prognose van HF patiënten verbeteren. Ook ziektemanagement programma's zijn beschikbaar met als doel de zelfzorg, kennis, leefstijl, therapietrouw, en de controle van de vitale functies (zoals bloeddruk, hartslag, en het lichaamsgewicht) te optimaliseren. Hoewel deze programma's effectief zijn, vragen ze veel tijd en personeel met als gevolg dat relatief weinig patiënten per hulpverlener geholpen kunnen worden. Gezien de bezuinigingen in de gezondheidszorg, in het bijzonder met het oog op het toenemend aantal oudere volwassenen, is er een internationale behoefte aan efficiëntere zorg voor mensen met HF. Een oplossing is om delen van de ziekte management programma's te vervangen door e-health. Dit lijkt zeker haalbaar in stabiele HF patiënten (dat wil zeggen patiënten die voldoende kennis hebben van HF en ingesteld zijn op HF medicijnen). Daarnaast kan e-health de autonomie en het zelfzorg gedrag van de patiënt verbeteren, en dit kan helpen om ongeplande ziekenhuisopnames te voorkomen.
Wat betreft literatuur rapporteerden studies over het effect van e-health bij HF tot nu toe inconsistente resultaten, en de meeste studies pasten e-health niet toe als vervanging van standaard zorg, maar als toevoeging aan de standaard zorg. Wat het effect is van interventies die de standaard zorg vervangen door e-health is momenteel onbekend. Ook hebben voorgaande studies niet het effect op zelfzorg gedrag gemeten, terwijl de zelfzorg gedrag – zij het een uitdagend begrip om te meten en te interpreteren - een meer 'natuurlijk' eindpunt is voor e-health interventies die gericht zijn op gedragsverandering.
Het voornaamste doel van dit proefschrift was om het effect op het zelfzorg gedrag en de kosteneffectiviteit van de twee e-health interventies, waarvan één met vervanging van de standaard zorg door e-health, bij HF patiënten te meten door middel van de e-Vita HF studie. Daarnaast beschrijven we het wereldwijde gebruik van één van de e-health oplossingen gebruikt in de interventies. Tot slot geven we informatie over hoe de resultaten op het zelfzorg gedrag van het studie geïnterpreteerd moeten worden en gaan we in op de generaliseerbaarheid van de resultaten.
In **hoofdstuk 2** beschrijven we de achtergrond, de doelstellingen, het wereldwijde gebruik, de geleerde lessen en de toekomstplannen van één van de e-health oplossingen die we onderzocht hebben in het e-Vita HF studie: de 'heartfailurematters.org' website (HFM website), een website met betrouwbare informatie over HF. In 2007 heeft de Hartfalen

vereniging (HFA) van de Europese vereniging van cardiologie (ESC) deze website gelanceerd. Het bevat informatie voor patiënten, hun mantelzorgers, professionals in de gezondheidszorg, en het grote publiek. Het is bedoeld als een praktisch hulpmiddel voor wereldwijd gebruik met advies en richtlijnen over het leven met HF. De website is nu beschikbaar in negen talen. Het aantal bezoeken, gemeten met Google analytics, werd gebruikt om het gebruik van de HFM website weer te geven van 2010 tot 2016.

Wereldwijd steeg het aantal bezoeken per jaar, van 416.345 in 2010 naar 1.636.368 in 2015. Het grootste aantal gebruikers (72-75%) vond de site met behulp van een zoekmachine. Desktops en meer recent ook smartphones werden gebruikt om de website te bezoeken; in 2015 met respectievelijk 50% en 38%. Hoewel de HFM website steeds vaker bezocht wordt, heeft het zijn volledig potentieel nog niet bereikt: minder dan 2 miljoen gebruikers brachten een bezoek aan de website, in tegenstelling tot naar schatting 23 miljoen mensen met HF wereldwijd. Het gebruik kan worden verbeterd door een doorlopend proces van kwalitatieve beoordeling van de voorkeuren van gebruikers, helpdesk faciliteiten, en uitgebreide IT en promotionele ondersteuning.

Hoofdstuk 3 bevat informatie over de interpreteerbaarheid van de Europese Hartfalen Zelfzorg gedrag schaal (EHFScBs) score, een gevalideerde vragenlijst om zelfzorg gedrag bij HF patiënten te meten. De vragenlijst wordt door de patiënt zelf ingevuld. Bij de 1023 deelnemers van de COACH studie (uitgevoerd van 2002 tot 2007 in Nederland), hebben we gekeken naar de verdeling van de EHFScBs scores. Dit biedt informatie over of de studiepopulatie en subgroepen gemiddeld een lage of een hoge score laten zien. De EHFScB scores waren op dezelfde wijze normaal verdeeld onder de studiepopulatie en de klinisch relevante subgroepen (bijvoorbeeld leeftijd (<60, tussen 60 en 80, ≥80 jaar), geslacht (vrouw, man), burgerlijke staat (met een partner, single)), met een gemiddelde tussen 57,8 (SD 19,4) en 72,0 (SD 18,0).

Daarnaast bleek een afkappunt van 70 onderscheidend voor patiënten met voldoende en onvoldoende zelfzorg; bij de deelnemers met een score van 70 was het aantal ziekenhuis opnames (ongeacht oorzaak) significant lager dan bij de resterende 559 patiënten met onvoldoende zelfzorg gedrag (minder dan 70 op de EHFScBs).

Hoofdstuk 4 bevat een beschrijving van de rationale, het ontwerp, de studiepopulatie, de powerberekening, het werven van patiënten, de interventies, de eindpunten en de statistische analyses van de e-Vita HF studie. In de e-Vita HF studie, wilden wij kijken naar het effect op het zelfzorg gedrag van (1) de website ESC / HFA heartfailurematters.org 'on top of' de standaard zorg, en (2) een e-health aangepast zorgpad met vervanging van de routine consultaties met de HF verpleegkundige in stabiele HF patiënten. Tenslotte wilden wij de kosteneffectiviteit van deze interventies evalueren. Een gerandomiseerde studie met drie groepen werd uitgevoerd. Groep 1 ontving de standaard zorg; groep 2 standaard zorg plus de HFM website; en groep 3 een aangepast zorgpad met een interactief platform voor ziektemanagement (e-Vita

platform), inclusief een link naar de HFM website en telemonitoring faciliteiten, waarbij routine consultaties met de HF verpleegkundige op de polikliniek werden vervangen. In totaal waren 414 patiënten nodig, geworven bij 10 Nederlandse HF poliklinieken of huisartspraktijken, om een effect aan te tonen. De deelnemers werden 12 maanden gevolgd. De patiënten werden ingesloten in de studie als ze een HF diagnose gekregen hadden ten minste 3 maanden voor aanvang. Daarnaast was toegang tot internet, e-mail en vaardigheden om ermee om te gaan een vereiste. Het primaire eindpunt was zelfzorg gedrag, zoals gemeten met de EHFScB schaal. Secundaire eindpunten waren kwaliteit van leven, cardiovasculaire- en HF-gerelateerde sterfte, ziekenhuisopname, en de duur ervan zoals vastgelegd door ziekenhuis en huisartsen registraties, het gebruik van en de tevredenheid van de gebruiker met de HFM website, en de kosteneffectiviteit.

Hoofdstuk 5 beschrijft de resultaten van de e-Vita HF studie. In totaal namen 450 (150 per groep) patiënten deel aan de studie. De gemiddelde leeftijd was 66,8 (SD 11,0) jaar, 74,2% was man en 78,8% geclassificeerd als NYHA I of II bij aanvang. Na 3 maanden follow-up, was de gemiddelde score op de zelfzorg gedrag schaal significant hoger in de groep met de website en het aangepaste zorgpad vergeleken met de groep met standaard zorg: 73,5 versus 70,8 (verschil 2,7, 95% BI 0,6-6,2) en 78,2 versus 70,8 (verschil 7,4, 95% BI 3,8-9,4), respectievelijk. Het effect werd minder gedurende de volgende 9 maanden tot er geen verschillen meer waren tussen de groepen na één jaar (verschil-0.6, 95% BI-3,7- 3,4 en 3,4 95% BI-0,7- 6,4, respectievelijk). Kwaliteit van leven en HF kennis lieten vergelijkbare resultaten als op zelfzorg gedrag zien. Voor de andere secundaire eindpunten lieten de groepen geen duidelijke verschillen zien.

In **hoofdstuk 6** wordt de kosteneffectiviteit van het e-Vita HF studie weergegeven. De mate van gezondheid van de patiënt werd gemeten met de EuroQol-5D-5L vragenlijst op baseline, en na 3, 6 en 12 maanden. Gegevens over de gezondheidszorgkosten werden verzameld uit de dossiers van ziekenhuizen en huisartsen. De analyses werden uitgevoerd vanuit het gezondheidszorg perspectief. Bootstrapping werd gebruikt om de onzekerheid rondom de eindpunten te bepalen. The analyse toonde aan dat de gemiddelde effecten op de gezondheid in termen van een, voor kwaliteit van leven gecorrigeerd, levensjaar (QALY) (bereik 0-1) 0,73, 0,74, 0,76 QALY was voor de standaard zorg, website, en de e-health aangepast zorgpad groep, respectievelijk. De overeenkomstige gemiddelde kosten per patiënt waren € 5.741, € 4.865 en € 5.111. Het netto monetaire voordeel was positief (groter dan 0) voor zowel de website en de e-health aangepaste zorgpad groep ten opzichte van de standaard zorg groep bij een betalingsbereidheid van € 80.000 / QALY. Voor een betalingsbereidheid van maximaal € 15.000 / QALY, had de website groep de grootste kans om kosteneffectief te zijn. Bij een betalingsbereidheid van € 15.000 / QALY of meer, had de e-health aangepaste zorgpad groep de grootste kans kosteneffectief te zijn. Kortom, de invoering van de heartfailurematters.org website in ambulante zorg in HF resulteert in een kleine toename in gezondheid, terwijl het

kosten vermindert. Het e-health aangepaste zorgpad met telemonitoring faciliteiten kan een bijkomend effect op de gezondheid bewerkstellingen tegen een beperkte kostentoename.
In **hoofdstuk 7** beschrijven we de representativiteit van de patiënten in e-health gerandomiseerde gecontroleerde onderzoeken. We hebben de eigenschappen van de deelnemers met niet-deelnemers in de e-Vita HF studie vergeleken. We vergeleken ook de kenmerken van e-Vita HF deelnemers met de studiepopulatie van andere gepubliceerde gerandomiseerde HF e-health studies die eerder uitgevoerd zijn en samengevat zijn in een recent gepubliceerde review van Cochrane. Een aselecte steekproef van 405 e-Vita HF deelnemers werd gebruikt voor de analyses. Deze groep werd vergeleken met een aselecte steekproef van niet-deelnemers (n = 402). Demografische en ziekte-specifieke kenmerken van de deelnemers en niet-deelnemers werden verzameld op baseline. Deelnemers waren jonger (gemiddelde leeftijd 66,7 versus 73,4 jaar, p <0,001), vaker man (75% vs. 58%, p <0,001) en hadden in het algemeen minder andere aandoeningen. Na correctie voor leeftijd, kwamen bloedarmoede en angina pectoris niet meer veel minder voor bij deelnemers ten opzichte van niet-deelnemers, terwijl SES nu significant hoger was bij de deelnemers in vergelijking met niet-deelnemers. In de Cochrane studies was de gemiddelde leeftijd van de deelnemers 68 jaar (tussen 54-78 jaar), 73% (tussen 35-85%) was man, 30% (4-43%) had diabetes en 43% (15-67%) bekend met hypertensie. Deze eigenschappen waren vergelijkbaar met de deelnemers van de e-Vita HF trial.
In **hoofdstuk 8**, de algemene discussie, vatten we de belangrijkste bevindingen van dit proefschrift samen. Daarnaast gaan we in op drie aspecten van e-health in de zorg voor HF die extra aandacht behoeven om de zorg verder te verbeteren en efficiënter te maken. Als eerste bespreken we hoe we het korte-termijn effect van e-health oplossingen kunnen handhaven, ofwel hoe een verandering in zelfzorg gedrag met e-health interventies op de lange termijn bewerkstelligd zou kunnen worden. Volgens de literatuur, zouden vooraf vastgestelde dialogen en vragen over HF symptomen, HF kennis en HF gerelateerd gedrag het aangepaste zelfzorg gedrag kunnen onderhouden. Ook het gebruik van de Theorie van gepland gedrag (TPB) lijkt zinvol bij het ontwerpen van een e-health interventie om een langdurig effect op zelfzorg gedrag te bereiken. Ten tweede bespreken we de noodzaak om vrij toegankelijke medische websites te evalueren en bij te werken. In Nederland zijn een aantal vrij toegankelijke medische websites met geloofwaardige en onafhankelijke informatie over de symptomen, ziekten, gezondheid en medicijnen erg populair. Een mooi voorbeeld is Thuisarts.nl, een website gericht op het informeren van patiënten over hoe om te gaan met veel voorkomende klachten, zoals hoesten of een zere keel. Deze websites verminderen de werklast van zorgverleners in de gezondheidszorg enorm. Met de toenemende interesse van mensen in websites met medische informatie is het regelmatig evalueren van zulke websites belangrijk om te beoordelen of hun doelstellingen worden gehaald. In dit tijdperk, waarin de ICT snelle ontwikkelingen doormaakt op het gebied van gebruiksvriendelijkheid kan de

mate waarin aan de doelstellingen van een website wordt voldaan snel verminderen door concurrerende meer gebruiksvriendelijke websites (met misschien zelfs minder betrouwbare informatie). De bestaande medische websites worden op dit moment helaas niet regelmatig geëvalueerd, terwijl dit de geloofwaardigheid en de impact van de sites kan verbeteren. Om de invloed van geloofwaardige en vrij toegankelijke medische websites te verhogen, is het daarnaast ook van belang dat hulpverleners en andere stakeholders dit naar (potentiële) gebruikers communiceren. Zo kan een certificaat op de website van een betrouwbare certificerende instantie (zoals de Health on the Net (HON)) helpen.

Als laatste, bespreken we of de tijd rijp is om face-to-face consultaties met de HF verpleegkundige te vervangen door e-health interventies in stabiele patiënten met HF. Op dit moment kunnen we nog niet concluderen dat de e-health interventies even veilig zijn als de standaard zorg. We kunnen alleen maar concluderen dat geen van de eerder uitgevoerde relevante studies (d.w.z. e-Vita HF, INTOUCH en TEHAF) een verhoogd risico liet zien op bijvoorbeeld ziekenhuisopnames en/of sterfte. Echter, om de veiligheid te bewijzen is een onderzoek nodig met een 'non-inferiority' opzet. Dit is de opzet om te onderzoeken of het effect van een e-health interventie niet slechter is (niet onveiliger) dan de standaard zorg. Hiervoor is echter een grote studiepopulatie nodig. Het samenvoegen van de gegevens van individuele patiënten van beschikbare studies en het uitvoeren van een IPD meta-analyse kan een alternatief zijn om de studiepopulatie te vergroten en de veiligheid te beoordelen. Concluderend, het korte termijn effect van e-health oplossingen in HF patiënten kan mogelijk worden gehandhaafd door het integreren van een gedragsmodel en een duidelijke proactieve aanpak met op maat gemaakte push-berichten. Het is belangrijk om vrij toegankelijke medische websites te evalueren en hun geloofwaardigheid communiceren naar patiënten en mantelzorgers. Om te beslissen over vervanging van face-to-face zorg door e-health is nader onderzoek naar de veiligheid nodig. Dit is de moeite waard omdat een dergelijke strategie kosteneffectief lijkt.

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Curriculum Vitae

Kim Pieternella Wagenaar was born on May 4th, 1984 in Hilversum, the Netherlands.

She obtained her nursing degree in 2007. From 2007 to 2012 she worked as a nurse at the cardiology department in the University Medical Center Utrecht. Besides her enthusiasm for the nursing profession Kim developed a special interest in research. During her work at the cardiology department she started the Master 'Health Sciences' at the VU University (specialization: Prevention and Public Health), and graduated in 2011.
Kim conducted her final internship for Health Sciences in Paris on socioeconomic differences in respiratory cancers at INSERM (a French research institute in medical research and public health). After her graduation she continued working there as a junior researcher.

In March 2012 she started her PhD track at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, on e-health in heart failure patients. In her PhD track she combined her expertise obtained as a nurse at the cardiology department with her research skills. This resulted in the work presented in this thesis. During her PhD track she also acquired the postgraduate Master degree in Epidemiology in 2016. Since January 2017, she works as a scientific advisor at the European Association of Preventive Cardiology from the ESC.