Original Article

Disease management with home telemonitoring aimed at substitution of usual care in the Netherlands: Post-hoc analyses of the e-Vita HF study

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ABSTRACT

Background: Home telemonitoring in heart failure (HF) patients may reduce workload of HF nurses by reducing face-to-face contacts. The aim of this study is to assess whether telemonitoring as a substitution could have negative effects as expressed by less reduction in circulating natriuretic peptide levels between baseline and one-year of follow up compared to usual care.
Methods: A post-hoc analysis of the e-Vita HF trial, a three-arm parallel randomized trial conducted in stable HF patients. Patients were randomized into three arms: (i) usual HF outpatient care, (ii) usual care combined with the use of the website heartfailurematters.org, and (iii) telemonitoring (e-Vita HF platform) instead of face-to-face consultations. Mixed linear model analyses were applied to assess differences in the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels between the three arms over a year.
Results: A total of 223 participants could be included (mean age 67.1 ± 10.1 years, 27% women, New York Heart Association class I–IV; 39%, 38%, 14%, and 9%). The mean left ventricular ejection fraction was 35 ± 10%. The median of routine face-to-face contacts over a year was 1.0 lower (2.0 vs. 3.0) in the third arm compared with usual care. Median NT-proBNP levels did not significantly differ between the three arms.
Conclusion: In stable and optimally treated HF patients, telemonitoring causing a reduction of routine face-to-face contacts seems not to negatively affect hemodynamic status as measured by NT-proBNP levels over time.

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Introduction

In the Netherlands, nurse-led multidisciplinary heart failure (HF) disease management programmes are intensive, with on average, three times face-to-face contacts a year with HF nurses and, once yearly, a consultation with a cardiologist specialised in HF [1]. Much attention is paid to adherence to medical therapy, education, lifestyle, and applying monitoring tailored to each individual HF

patient [2,3]. Non-invasive home telemonitoring could be an important component of HF disease management by facilitating remote support to patients and by helping patients and healthcare professionals to early detection of worsening of HF. Ideally, home telemonitoring could be used to substitute face-to-face contacts and thus prevent work overload of HF nurses and reduce travelling of patients to the hospital.

Previous randomized clinical trials (RCTs) on the effectiveness of home telemonitoring in HF evaluated such telemonitoring *in addition to* usual care [4–6]. Only a few studies showed a relatively small beneficial effect on (cardiovascular) mortality and HF hos-

pitalization, notably *only if* the usual care was not of the highest level [7,8]. However, also the type of home telemonitoring and the case mix (severity of disease state, stable vs. unstable patients, etc.) contributed to these differences in outcomes between previous studies. HF home telemonitoring should focus either on those who easily deteriorate, with the aim to safely prevent HF re-admissions [9], or -rather the opposite- it should focus on stable HF patients [mainly in New York Heart Association (NYHA) class I and II with optimal treatment] and then aimed at reducing the number of routine face-to-face contacts with HF nurses [1].

It is well known that an individual's increase in B-type natriuretic peptide (BNP) levels is associated with the risk of adverse clinical events [10–12]. Therefore, changes in natriuretic peptides levels can be used as a surrogate outcome in HF studies. Currently, it is unknown whether reducing face-to-face contacts by increasing home telemonitoring in HF may have negative effects, which could be uncovered by increase in circulating natriuretic peptides levels over time compared to usual care.

The e-Vita HF trial evaluated stable HF patients who had been managed for >3 months in Dutch HF dedicated outpatient clinics [1,13]. In the three arm RCT, (i) an e-health adjusted care pathway (EACP), including an interactive platform for HF disease management (the e-Vita platform) with telemonitoring facilities plus the website heartfailurematters.org (HFM) was compared to (ii) usual care and (iii) usual care plus access to the website HFM [1,13]. The explicit aim of EACP was to replace routine consultations to prevent work overload of HF nurses, which otherwise may occur in case home telemonitoring were added to standard care [13]. This resulted in a reduction in the median number of routine contacts between the EACP group and the usual care group (median 2.0 vs. 3.0/year) [1].

The aim of this post-hoc analysis of the e-Vita HF trial was to assess changes over time of circulating natriuretic peptide levels [amino-terminal (NT) pro BNP] between the three arms of the e-Vita HF trial.

Methods

The design of the e-Vita HF study was described previously [13]. In short, the e-Vita HF study was a three-arm parallel randomized trial in 450 *stable* chronic HF patients, with in each arm 150 patients managed in 9 HF outpatient clinics in the Netherlands. The primary endpoint was self-care as measured with the European Heart Failure Self-care Behavior (EHFScB) scale. Self-care improved in the EACP arm compared to usual care at 3 months, but this effect attenuated during the remaining follow up of 9 months [1]. One of the secondary outcomes was health-related quality of life as measured with the Minnesota Living with Heart Failure Questionnaire, and a similar trend was seen over time [1].

In this study, EAPC was compared to (i) usual care and (ii) usual care plus HFM. In the EAPC arm, biometric values (blood pressure, weight, pulse) were automatically forwarded to the e-Vita platform using Bluetooth. If these values were outside the predefined thresholds or if the measurements were not recorded, the HF nurse received an alert via the e-Vita platform. No routine face-to-face consultations with the HF nurse were scheduled, but, if needed, the patient could contact the nurse.

Patient population

Eligible patients were aged 18 years or older, diagnosed with HF for at least 3 months, and had sufficient cognitive and physical function. Exclusion criteria were non-availability of internet and email, inability of the patient or his/her family to work with internet and email, inability of the patient or his/her family or care takers to read and understand Dutch.

In the e-Vita HF trial, either BNP or NT-proBNP values were measured. We did not include BNP because BNP and NT-proBNP differ with regard to their biological activity and half-life, *in vitro* stability, and clearance mechanisms. There were 23 missing baseline NT-proBNP values (usual care: *n* = 8, usual care plus website: *n* = 8, EACP: *n* = 7) and because of the low number, these were imputed, but the 86 missing values at 6 and/or 12 months were not (see Fig. 1). Patients with missing NT-proBNP values at 6 and/or 12 months were excluded, because the delta could not be calculated. The missing NT-proBNP values occurred due to logistical problems in the participating hospitals, and in one batch containing 55 samples because the central laboratory did not handle the blood adequately. Because 23 patients died within the year of the follow up, in total 223 patients could be analyzed (Fig. 1). The baseline characteristics of these 223 patients did not differ from the 227 who were not included in this post-hoc analysis (Online Table 1).

Statistical analyses

Continuous variables with a normal distribution are expressed with means and standard deviation (SD). NT-proBNP and estimated glomerular filtration rate (eGFR) levels (skewed distribution) are presented as medians with interquartile range (IQR). For further analysis, we used log transformations to achieve a more normal distribution.

Because performing a complete case analysis (deleting all patients with one or more missing values from the analysis) may lead to bias and lack of power, we decided to multiple impute missing baseline NT-proBNP values [14]. Multiple imputation was performed to impute missing baseline values only. For this, we used predictive mean matching for continuous variables, and regression methods for categorical variables. We created 25 imputed datasets and performed the analyses on each imputation set separately. The presented results are based on pooled estimates.

Differences in NT-proBNP levels (between baseline and 6 and 12 months) in the EACP group were compared to (i) usual care, and (ii) usual care plus HFM using a linear mixed model. We included a random intercept to correct any differences between patients from different hospitals and a residual covariance (GEE type) matrix to correct repeated measurements of the outcome (NT-proBNP) over time. The validity of the models (distributional assumptions, homoscedasticity) was assessed with residual plots.

All analyses were performed in two steps: In the first step only the three arms and time points (baseline, 6 and 12 months) were included in the model. In the second step, we added the baseline measurements of the outcome as well as age, gender, body mass index, history of atrial fibrillation, history of acute coronary syndrome, patient-reported NYHA class, left ventricular ejection fraction, and eGFR as potential confounders.

Results

Of the original 450 patients, 223 patients could be analyzed for delta NT-proBNP values over a year (Fig. 1). The mean age of the 223 patients was 67.1 ± 10.1 years and 27% were women (Table 1). The mean left ventricular ejection fraction was 34 ± 10%, and the majority of patients had a low patient-reported NYHA class: I 39%, II 38%, III 14%, and IV 9%, respectively. Forty-five percent of the patients had a history of an acute coronary syndrome and 41% of atrial fibrillation. The median eGFR was 68 (IQR 52–85) ml/min/1.73 m^2. The median face-to-face visits with the HF nurse in the e-Vita HF arm compared to usual care was 2.0 (IQR 1.0–3.0) vs. 3.0 (IQR 2.0–4.0). In the six months before enrolment in the trial, 11% of the 223 participants were re-hospitalized for worsening HF. In patients with NYHA class I, the combination of
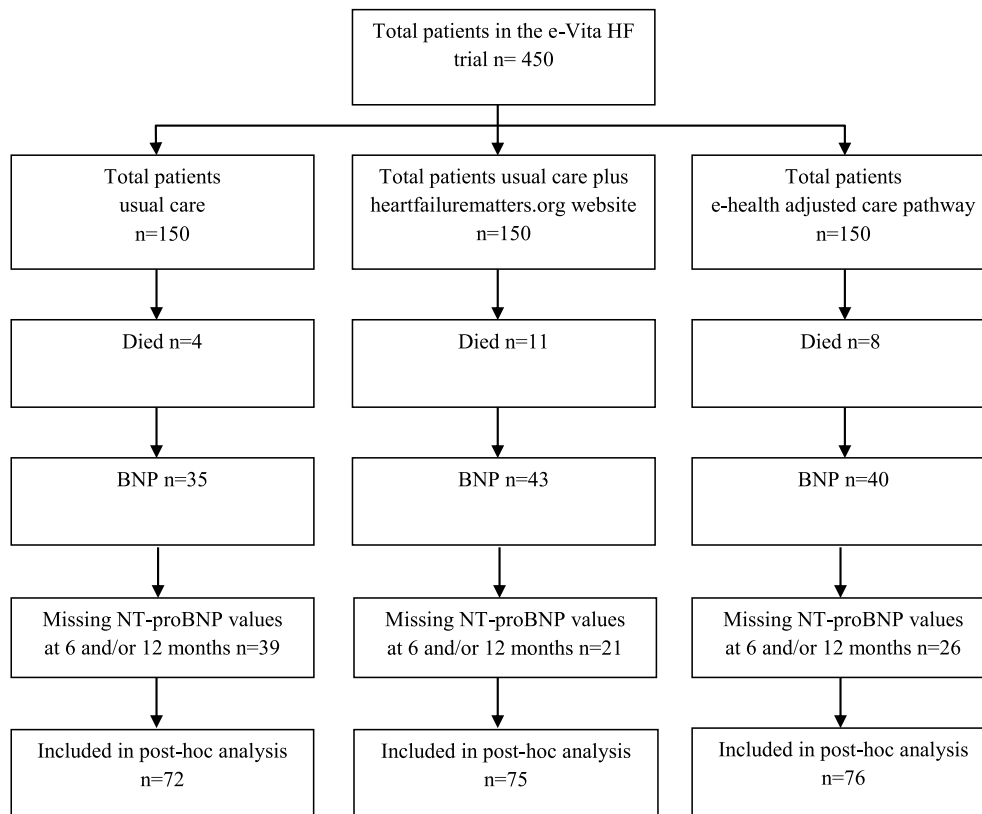
Fig. 1.. Flow chart of study patients of the post-hoc analysis.
NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) with a beta-blocker was prescribed to 74% of the patients. In 38% of those with NYHA class II or higher, the combination ACE inhibitor or ARB with beta-blocker and a mineralocorticoid receptor antagonist (MRA) was prescribed.

Median NT-proBNP values were low on average. There was a reduction in NT-proBNP levels during the one-year study period: in all 223 participants, the median at baseline was 119 pg/ml (IQR 43–310) and at 12 months 91 pg/ml (IQR 32–275). The delta reduction in NT-proBNP was 26 pg/ml in the EAPC arm versus 7 pg/ml in the usual care arm (Table 2). After linear mixed modelling, there were no significant differences in the median log NT-proBNP levels (at baseline and after 6 and 12 months) between the EACP arm and usual care arm (Table 3).

Discussion

In this study, we showed that a reduction of 33% in scheduled face-to-face contacts in the EAPC arm did not have a negative impact on NT-proBNP levels over the course of one year when compared to (high intensity) usual multidisciplinary HF outpatient care. Importantly, this result was seen in stable HF patients. The percentage of re-admissions for worsening HF in the 6 months before enrolment in the randomized trial was low (11%) and the vast majority of patients had a low patient-reported NYHA class (77% NYHA class I or II) under treatment. In 74% of the patients with NYHA class I an ACE inhibitor or ARB with beta-blocker was prescribed, and in 38% of the patients with NYHA class II or over, an ACE inhibitor or ARB with beta-blocker and MRA. Interpreting these results, one should realize from the 2012 ESC guidelines on heart failure onwards, MRAs were recommended in symptomatic

HF patients (NYHA class $\geq$ II and left ventricular ejection fraction <35%), and that the uptake of new recommendations in everyday practice takes time.

Background of home telemonitoring in the Netherlands

In the Netherlands, most HF patients managed in multidisciplinary HF outpatient clinics receive intensive care with three times a year routine face-to-face contacts with a HF nurse and a yearly consultation with a cardiologist with special interest in HF, similarly as seen in the-Vita HF study (mean of 3.2 contacts) [1]. The government and health insurance companies stimulate the use of home telemonitoring in HF with the aim of reducing costs, while patient organizations 'embrace' telemonitoring because it could improve self-care and self-confidence of patients. Nevertheless, home telemonitoring in HF is still not widely implemented in HF care. Barriers include financial incentives for the transition of care to an EAPC to compensate for the time investment of health care professionals, and the lack of an evident mortality-reducing effect of home telemonitoring in addition to or as a partly substitute for the standard of care.

Previous Dutch home telemonitoring research in HF mainly focused on reduction of HF (re)admissions

Our study builds on the results of five former studies that evaluated non-invasive home telemonitoring in HF in the Netherlands [9,15–18]. Comparison of these studies is hampered by differences in methods, case mix, and interventions. Nevertheless, none of these studies showed significant beneficial effects on (cardiovascular) death or HF hospitalization [1,9,16–19]. All studies, except the

Table 1

Baseline characteristics of 223 patients, divided in usual care, usual care with guided access to the heartfailurematters.org website, and e-health adjusted care pathway.

Baseline characteristics	Arm 1, usual care (n = 72)	Arm 2, usual care with heartfailurematters.org website (n = 75)	Arm 3, e-health adjusted care pathway (n = 76)	p-value
Demographics				
Mean age in years ± SD	68.2 ± 11.6	67.3 ± 9.2	65.8 ± 9.6	0.34
Female sex, %	29.2	29.3	24.0	0.68
Mean BMI ± SD	28 ± 4	28 ± 5	29 ± 5	0.50
Medical history				
Acute coronary syndrome, %	48.6	40.0	46.1	0.56
Atrial fibrillation, %	33.3	48.0	39.5	0.19
Renal disease, %	12.5	17.3	13.2	0.66
Mean LVEF ± SD	36 ± 10	35 ± 11	33 ± 10	0.20
Hospitalization HF in the 6 months before start of the study, %	12.5	12.0	9.2	0.79
Patient-reported NYHA class at baseline, %				0.15
I	40.3	33.3	44.7	
II	36.1	38.7	39.5	
III	19.4	13.3	9.2	
IV	4.2	14.7	6.6	
Medication use				
ACEI, %	50.0	57.3	53.9	0.71
ARBs, %	33.3	28.0	22.4	0.33
Beta-blockers, %	84.7	84.0	80.3	0.74
MRAs, %	44.4	44.0	44.7	0.99
ACEI and/or ARBs plus Beta-blockers, %	72.2	72.0	73.7	0.97
Loop diuretics, %	80.6	81.3	73.7	0.18
Laboratory results				
Median eGFR ml/min/1.73m^2 (25th–75th percentiles)	68 (51–83)	65 (51–87)	69 (57–84)	0.56
Questionnaires				
Self-care behavior score*, mean EHFScBS total score ± SD	71.9 ± 14	70.1 ± 16	71.8 ± 14.5	0.71
Quality of life, mean Minnesota Living with Heart Failure Questionnaire**, total score ± SD	27.1 ± 19.7	27.4 ± 18.8	25.2 ± 19.0	0.78

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; *the European Heart Failure Self-Care Behavior Scale (EHFScBS) consists of nine items on a 5-point Likert scale with standardized score 0 to 100, with a higher score meaning better self-care; ** the Minnesota Living with Heart Failure Questionnaire consists of twenty-one items on a 5-point Likert scale with standardized score 0 to 105, with lower scores meaning better health related quality of life.

Table 2

Median N-terminal prohormone of brain natriuretic peptide values in pg/ml with 25th–75th percentiles at baseline, 6, and 12 months.

	Usual care (n = 72)	Usual care + heartfailurematters.org website (n = 75)	e-health adjusted care pathway (n = 76)
Baseline	96 (32–307)	121 (40–309)	109 (38–310)
6 months	108 (36–232)	108 (46–222)	89 (40–185)
12 months	89 (32–282)	93 (34–287)	83 (25–259)

Table 3

Mixed linear model presented on a log transformed scale, with **N-terminal prohormone of brain natriuretic peptide** unadjusted and adjusted for baseline differences in age, gender, body mass index, history of atrial fibrillation, history of acute coronary syndrome, self-reported NYHA class, LVEF, and eGFR.

Comparison arms	Unadjusted		Adjusted	
	Difference in regression coefficient (95% CI)	p-value	Difference in regression coefficient (95% CI)	p-value
Usual care versus **usual care + heartfailurematters.org website**	0.11 (-0.27 - 0.48)	0.58	- 0.08 (-0.16 - -0.05)	0.59
Usual care versus **e-health adjusted care pathway**	- 0.15 (-0.52 - 0.22)	0.43	- 0.20 (-0.30 - -0.11)	0.15
Usual care + heartfailurematters.org website versus **e-health adjusted care pathway**	- 0.26 (-0.63- 0.12)	0.18	- 0.13 (-0.23 - -0.01)	0.38

Both models were corrected for differences between participants from different hospitals.

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e-Vita HF trial, focused on patients who easily deteriorate and were aimed to prevent HF re-admissions. Four studies provided home telemonitoring in addition to usual care and two (e-Vita HF and IN TOUCH) aimed at (partly) substitution for care [1,15].

The e-Vita HF trial is the only study with a focus on reducing the number of routine face-to-face contacts in stable HF patients [1].

Home telemonitoring and the COVID-19 pandemic

The COVID-19 pandemic has put enormous pressure on health care systems worldwide, and with teleconsultation routine face-to-face contacts could be substituted. Home monitoring with pulse oximetry of patients with COVID-19 appeared to be useful to early detect clinical deterioration due to (silent) hypoxemia. Because HF patients have a more than 10 times higher risk for hospitalization for COVID-19, home oxygen monitoring is worthwhile. The COVID-19 pandemic offered a boost to digitalizing health care, and eHealth may substitute at least a part of the time-consuming face-to-face routine care contacts.

Limitations

This study has several limitations. First, the current post-hoc analysis was performed in a fraction of the original population of the e-Vita HF trial. However, this selection did not seem to result in selection bias, because the baseline characteristics of included and excluded patients were similar.

Second, our results in the EAPC arm cannot straightforwardly be generalized to unstable HF patients. Third, NT-proBNP values depend on multiple variables, not only on severity of heart failure. Atrial fibrillation also results in increased left atrial and ventricular wall stress and thus elevated NT-proBNP values. Fourth, we did not register the number of patients who developed new-onset atrial fibrillation during the one year of follow up. However, given the incidence rate of atrial fibrillation in older people, it may be expected that no more than a few percent of patients developed new-onset atrial fibrillation within a year. Moreover, this likely would occur similarly in the different study arms, and thus would not introduce bias or affect our conclusion because we used delta NT-proBNP (change over time) and not the absolute NT-proBNP values.

Conclusion

An EAPC management strategy including home telemonitoring and aimed at reducing routine face-to-face contacts seems to be a good and likely cost-effective alternative for intensive HF nurse-led outpatient care of stable and well up-titrated HF patients.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2021.08.003.

References

[1] Wagenaar K, Broekhuizen BDL, Jaarsma T, Kok I, Mosterd A, Willems FF, et al. Effectiveness of the European society of cardiology/heart failure association website 'heartfailurematters.org' and an e-health adjusted care pathway in patients with stable heart failure: results of the 'e-Vita HF' randomized controlled trial. Eur J Heart Fail 2019;21:238–46.

[2] Jaarsma T, Haaijer-Ruskamp FM, Sturm H, van Veldhuisen DJ. Management of heart failure in The Netherlands. Eur J Heart Fail 2005;16(7):371–5.

[3] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129–200.

[4] Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JGF. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev 2015;10:CD007228.

[5] Son YJ, Lee Y, Lee HJ. Effectiveness of mobile phone-based interventions for improving health outcomes in patients with chronic heart failure: a systematic review and meta-analysis. Int J Environ Res Public Health 2020;17:1749–62.

[6] Eurlings C, Boyne JJ, de Boer RA, Brunner-La Rocca HP. Telemedicine in heart failure-more than nice to have? Neth Heart J 2019;27:5–15.

[7] Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. Lancet 2018;392:1047–57.

[8] Krum H, Forbes A, Yallop J, Driscoll A, Croucher J, Chan B, et al. Telephone support to rural and remote patients with heart failure: the chronic heart failure assessment by telephone (CHAT) study. Cardiovasc Ther 2013;31:230–7.

[9] Boyne JJ, Vrijhoef HJ, Crijns HJ, de Weerd G, Kragten J, Gorgels APM. Tailored telemonitoring in patients with heart failure: results of a multicentre randomized controlled trial. Eur J Heart Fail 2012;14:791–801.

[10] Linssen GCM, Jaarsma T, Hillege HL, Voors AA, van Veldhuisen DJ. A comparison of the prognostic value of BNP versus NT-proBNP after hospitalisation for heart failure. Neth Heart J 2018;26:486–92.

[11] Savarese G, Hage C, Orsini N, Dahlström U, Perrone-Filardi P, Rosano GMC, et al. Reductions in N-terminal pro-brain natriuretic peptide levels are associated with lower mortality and heart failure hospitalization rates in patients with heart failure with mid-range and preserved ejection fraction. Circ Heart Fail 2016;9:e003105.

[12] Zile MR, Claggett BL, Prescott MF, McMurray JJV, Packer M, Rouleau JL, et al. Prognostic implications of changes in N-terminal pro-B-type natriuretic peptide in patients with heart failure. J Am Coll Cardiol 2016;68:2425–36.

[13] Wagenaar KP, Broekhuizen BD, Dickstein K, Jaarsma T, Hoes AW, Rutten FH. 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. Eur J Heart Fail 2015;17:1310–16.

[14] Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087–91.

[15] de Vries AE, de Jong RM, van der Wal MH, Jaarsma T, van Dijk RB, Hillege HL. The value of INnovative ICT guided disease management combined with telemonitoring in OUtpatient clinics for chronic heart failure patients. Design and methodology of the IN TOUCH study: a multicenter randomised trial. BMC Health Serv Res 2011;11:167–74.

[16] Balk AH, Davidse W, van Dommelen P, Klaassen E, Caliskan K, van der Burgh P, et al. Tele-guidance of chronic heart failure patients enhances knowledge about the disease. A multi-centre, randomised controlled study. Eur J Heart Fail 2008;10:1136–42.

[17] Cleland JG, Louis AA, Rigby AS, Janssens U, Balk AH. Noninvasive home telemonitoring for patients with heart failure at high risk of recurrent admission and death: the trans-European network-home-care management system (TEN-HMS) study. J Am Coll Cardiol 2005;45:1654–64.

[18] Veenstra W, Op den Buijs J, Pauws S, Westerterp M, Nagelsmit M. Clinical effects of an optimised care program with telehealth in heart failure patients in a community hospital in the Netherlands. Neth Heart J 2015;23:334–40.

[19] Kraai I, de Vries AE, Vermeulen K, van Deursen V, van der Wal M, de Jong R, et al. The value of telemonitoring and ICT-guided disease management in heart failure: results from the IN TOUCH Study. Int J Med Inform 2016;85:53–60.