Tailored telemonitoring in patients with heart failure: results of a multicentre randomized controlled trial

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Aims	Recent increases in heart failure tend to overload the healthcare system. Consequently, there is a need for innovative strategies to reduce heart failure hospitalizations.
Methods and results	A multicentre randomized controlled trial was carried out to test the hypothesis that telemonitoring reduces heart failure hospitalizations during 1 year follow-up. The mean age of the 382 participating patients was 71.5 (32–93) years; the mean left ventricular ejection fraction was 0.38, and in 61% it was $\leq 0.45\%$. Mean time to first heart failure-related hospitalization was 161 days for the intervention group and 139 days for the usual-care group; hospitalizations occurred in 18 (9.1%) compared with 25 (13.5%) patients, with a total number of 24 and 43 hospitalizations, respectively [Kaplan–Meier $P = 0.151$, hazard ratio (HR) 0.65, 95% confidence interval (CI) 0.35–1.17]. Subgroup analysis of the primary endpoint showed benefits for three subgroups: duration of heart failure, having a pacemaker, and co-habiting. The combined endpoint of heart failure admission and all-cause mortality was similar for both groups (Kaplan–Meier $P = 0.641$, HR 0.89, 95% CI 0.69–1.83). No differences were found regarding secondary endpoints, except for the reduced number of face to face contacts with the heart failure nurse (Mann–Whitney $P < 0.001$). Mortality was 18 (9.1%) in the intervention group and 12 (6.5%) in the usual-care group (Mann–Whitney $P = 0.34$, Cox regression analysis $P = 0.82$).
Conclusion	No significant differences were found regarding the primary endpoint, possibly caused by a relative underpowering of the population combined with well-treated study groups. However, telemonitoring tends to reduce heart failure (re)admissions and significantly decreases contacts with specialized nurses. Further research with pre-specified groups, as found in the subgroup analysis, is needed. Trial registration: NCT00502255.
Keywords	Heart failure • Telemonitoring • Tailored care • RCT • Education

Introduction

The prevalence of heart failure is rising due to improved survival after acute cardiac events and ageing of the population.[1,2]

Multidisciplinary nurse-led heart failure clinics are able to reduce the frequent admissions seen in this condition.[3,4] Such disease management systems comprise many elements, being described in eight domains, among other methods of communication.[5]

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Telemonitoring is a promising development of the latter[3] which, however, may fail if used in isolation[6] or if focusing on vital signs only.[7,8] The Health-Buddy® is a telemonitoring system which is patient driven, collecting and providing tailored patient- and disease-specific information. Pilot data showed that adherence to treatment is improved by involving patients in the process and stimulating self-care.[9]

We performed a randomized study comparing this novel approach to telemonitoring with usual care, both within an existing comprehensive disease management system. We hypothesized that telemonitoring reduces heart failure hospitalizations compared with usual care.

Methods

Trial design

As described previously,[10] the TElemonitoring in HeArt Failure (TEHAF) study is a prospective open label, multicentre, randomized controlled trial with blinded endpoint evaluation, conducted at three hospitals in The Netherlands. Investigators and study personnel (except for data entry officers) were unaware of the treatment group results until database closure. The study is registered at Clinical-trials.gov (NCT00502255). Approval was obtained from the Medical Ethical Committee of the participating centres, according to the Declaration of Helsinki.[11] Written informed consent was obtained before randomization.

Study population

From October 2007 to December 2008, consecutive patients with heart failure in New York Heart Association (NYHA) class II–IV were included. Heart failure was defined as at least one episode of fluid retention requiring diuretics, either with an echocardiographic left ventricular ejection fraction $\leq 40\%$ or a preserved ejection fraction with diastolic dysfunction. Further inclusion criteria were age ≥ 18 years, capable of providing informed consent, and being treated by a heart failure nurse together with a cardiologist. Patients were excluded if operating the Health-Buddy® system was physically or cognitively impracticable or when their expected life span was <1 year. A prior admission for heart failure[8,12,13] was not a prerequisite for inclusion.

Patient recruitment and randomization procedure

We screened 870 consecutive patients during their planned visit to our heart failure clinics; 488 patients refused to participate or were ineligible. Thus 382, recruited at the heart failure outpatient clinic, were enrolled and assigned to a study arm, using a computer-generated randomization procedure, with stratification per centre.

Intervention and usual care

The patients in the intervention arm received a device, with a liquid crystal display and four keys, connected to a landline phone. Automatic transfer of vital signs was not part of the system. Heart rate and blood pressure for both groups were collected during regular face to face contacts. Daily pre-set dialogues were communicated about symptoms, knowledge, and behaviour, being answered by touching one of the keys and sent to a server and to the nurses' desktop. Incorrect answers to a knowledge or behaviour issue were automatically corrected by the device and were visible in the display. Responses were also transferred into risk profiles (low, medium, high).[10] Positive

Table 1 Overview of the programmes tailored to the patients' needs

	Symptoms	Education/ adherence	No. of days
Programme 1	+	+	90
Programme 2	+	+/−	30
Programme 3	−	+	90
Programme 4	−	−	180

+, strongly focused on; +/−, moderately focused on; −, less focused on.
Programme 1 consists of a high level of monitoring of symptoms and a high level of education: at the start all patients are allocated to this programme.
Programme 2 consists of a high level of monitoring symptoms and a lower level of education: patients allocated at this programme are indicated for intensive monitoring because of severe heart failure or many complaints. Also, patients after admission for heart failure were allocated to this programme. Their disease-specific education level allows a less intensive education programme.
Programme 3 consists of a low level of monitoring symptoms and a high level of education: patients with few complaints and a low disease-specific education level are allocated to this programme.
Programme 4 consists of a low level of monitoring symptoms and a low level of education: patients with few complaints and a high level of disease-specific education are allocated to this programme.
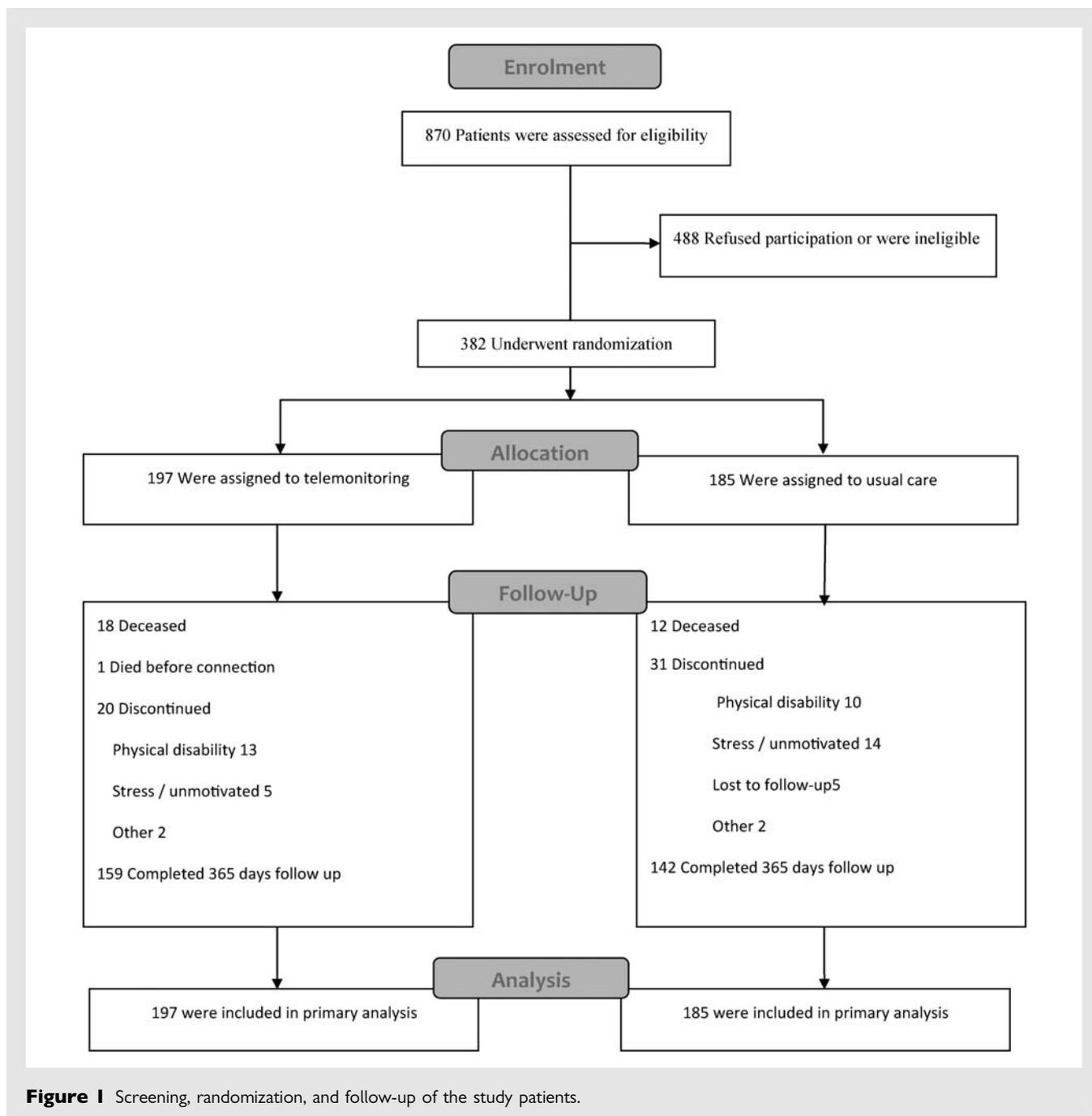
answers for symptoms triggered immediate responses by the heart failure nurse. The process was led by a heart failure nurse and a nurse assistant. The nurse assistant took care of educational and general high risks, such as persistent lack of adherence or symptoms of depression.[10]

In *Table 1* we present the four sets of dialogues with variable emphasis on symptoms or knowledge and behaviour, created to meet specific needs on treatment or education. All patients started with the initial set of dialogues which was evenly balanced for symptoms and education. After 3 months the dialogues were adjusted to the best fitting set for the current individual profile. Re-allocation to any of the other sets was possible at any time.[10] Following an admission for heart failure, re-allocation occurred to dialogues emphasizing symptom monitoring.

Nurse-led usual care was given according to the latest European Society of Cardiology (ESC) guidelines,[14] including oral and written educational information, and psychosocial support as needed. In the intervention group, two of four follow-up visits were skipped. Baseline characteristics were gathered at the first visit after enrolment. General and disease-specific information was also collected using a questionnaire. Follow-up was 1 year. Hospitalizations were identified during follow-up visits and by reviewing medical records. Data on hospitalization and mortality were collected by research nurses not involved in the patient care.

Outcomes

The primary outcome was time to first heart failure hospitalization, i.e. at least one overnight stay for a new episode or progression of fluid retention, with insufficient response to adjustment of oral medication, needing in-hospital intravenous treatment. Secondary outcomes included the combined endpoint of heart failure admission and all-cause death, the number of re-admissions for heart failure, all hospitalizations, and days in hospital for heart failure, cardiovascular (i.e. related to treatment or diagnostics of cardiac disease, or heart failure therapy related) and other-cause hospitalizations (i.e. not related to heart failure or cardiovascular), mortality, and number of visits to the heart failure clinic. An independent expert committee, blinded to study arm assignment, adjudicated heart failure-related

Enrolment

870 Patients were assessed for eligibility

488 Refused participation or were ineligible

382 Underwent randomization

Allocation

197 Were assigned to telemonitoring

185 Were assigned to usual care

Follow-Up

18 Deceased

1 Died before connection

20 Discontinued

  Physical disability 13

  Stress / unmotivated 5

  Other 2

159 Completed 365 days follow up

12 Deceased

31 Discontinued

  Physical disability 10

  Stress / unmotivated 14

  Lost to follow-up5

  Other 2

142 Completed 365 days follow up

Analysis

197 were included in primary analysis

185 were included in primary analysis

Figure 1 Screening, randomization, and follow-up of the study patients.

hospitalizations and deaths. Occasional differences in judgement were reconciled at a panel meeting and settled by the chairman in the case of non-unanimity.

Statistical analysis

The primary endpoint was summarized by treatment group and tested by the Kaplan–Meier time to event function. The 1 year admission rate within the usual-care arm was estimated at 25%.[15] To detect a 50% reduction from 25% to 12.5% in heart failure hospitalizations with a two-sided 95% significance, a power of 0.80, and 10% loss to follow-up, a sample size of 195 patients per group was needed. All analyses were performed on an intention-to-treat basis.

Interval and ratio variables were investigated for normality of distribution with the Shapiro–Wilk test. If normally distributed, means and standard deviations are given, otherwise score ranges are provided. Continuous variables are presented as median and interquartile ranges. Categorical variables are presented as frequencies and percentages. Univariate statistics on differences in baseline variables were calculated by the Student t-test if normally distributed, or, if not, by the Mann–Whitney test. Differences between categories in baseline factors were checked with log-likelihood χ^2. Secondary endpoints were calculated with the Mann–Whitney test, combined endpoint with the Kaplan–Meier, and mortality with the Cox regression analysis. All data analyses were performed using SPSS-pc version 16.0.

Table 2 Baseline characteristics

Variable	n	Intervention (197)	Control (185)	Total (382)	P-value
Age	382	71.0 ± 11.9	71.9 ± 10.5	71 ± 11	0.621
Range[a]		32−72−91	37−74−93		
Median	382	72 (63−81)	74 (65−80)	73 (64−80)	
≥ 75		88 (45)	85 (46)	173 (45)	0.199
Gender	382				0.747
Male		115 (58)	111 (60)	226 (59)	
Female		82 (42)	74 (40)	156 (41)	
Married/partner	379	122 (62)	123 (66)	245 (64)	0.265
Education	363				0.589
Primary school		63 (33)	59 (34)	122 (34)	
Second school/low vocational training		91 (48)	71 (41)	162 (45)	
Medium vocational training		19 (10)	23 (13)	42 (12)	
High vocational/university		17 (9)	20 (11)	37 (10)	
History of HF (months)[b]	382	19 (6−41)	17 (6−40)	18 (6−40)	0.413
HF history <18 months		98 (26)	98 (26)	196 (51)	
Range[a]		1−18−240	1−15−293		
NYHA classification/n (%)	382				0.404
NYHA II		110 (56)	109 (59)	219 (57)	
NYHA III		79 (40)	74 (40)	153 (40)	
NYHA IV		8 (4)	2 (1)	10 (3)	
Blood pressure[b]	382				
Systolic		120 (110−140)	125 (110−140)	123 (110−140)	0.156
Diastolic		72 ± 12.5	74 ± 12.2	73 (12)	0.193
Heart rate[b]	382	75 (68−85)	72 (68−85)	74 (65−85)	0.252
LBBB	382	20 (10.2)	22 (11.9)	42 (11)	0.587
Heart rhythm at baseline	382				
Sinus rhythm		96 (48.7)	113 (61.1)	209 (55)	0.015
Atrial fibrillation		62 (31.5)	35 (18.9)	97 (25)	0.007
Pacemaker rhythm		36 (18.3)	35 (18.9)	71 (18)	0.817
Other		3 (1.5)	2 (1.1)	5 (1)	n.a.
Echocardiography					
Ejection fraction[b]	374	36 (28−50)	35 (26−42)	36 (28−48)	0.751
Median ejection fraction		36	35	36	
Mitral regurgitation	375	122 (64)	121 (67)	243 (65)	0.345
Tricuspid regurgitation	375	102 (54)	86 (47)	188 (50)	0.381
Ischaemia	382	99 (50.3)	91 (49.2)	190 (50)	0.835
Pacemaker		59 (29.9)	53 (28.6)	112 (29)	0.147
DDD		15 (25)	19 (36)	34 (30)	
Biventricular		2 (3)	7 (13)	9 (8)	
ICD		14 (24)	11 (21)	25 (22)	
Biventricular ICD		24 (41)	14 (26)	38 (34)	
Other		4 (7)	2 (4)	6 (6)	
Blood samples (mmol/L)					
Sodium	382	140.1 ± 2.9	140.2 ± 2.9	140.1 ± 2.9)	0.779
Potassium	382	4.36 ± 0.5	4.37 ± 0.5	4.27 ± 0.5	0.873
Urea	382	11.18 ± 6.2	10.76 ± 5.6	10.9 ± 5.9	0.485
Creatinine (μmol/L)	382	128 ± 53.9	125 ± 55.3	127 ± 54.5	0.466
ProBNP[b]	145	313 ± 506	417 ± 561	365 ± 560	0.953
NT-proBNP[c]	131	2837 ± 5293	3229 ± 6003	3033 ± 5648	0.730
Haemoglobin	382	8.2 ± 1.1	8.2 ± 1.2	8.1 ± 1.1	0.950

Continued

Table 2 *Continued*

Variable	n	Intervention (197)	Control (185)	Total (382)	*P*-value
Medication					
Diuretics	380	170 (86)	163 (88)	333 (87)	0.783
ACE inhibitors	378	113 (58)	104 (57)	217 (57)	0.826
ATII antagonists	373	67 (35)	56 (31)	123 (33)	0.459
Beta-blockers	379	161 (82)	149 (81)	310 (82)	0.689
Digoxin	372	46 (24)	45 (25)	91 (24)	0.770
Nitrates	376	64 (33)	72 (39)	136 (36)	0.212
Statins	377	111 (57)	107 (58)	218 (57)	0.900
Coumarins	377	119 (61)	95 (52)	214 (57)	0.084
ASA	373	60 (31)	71 (39)	131 (35)	0.091
Charlson index[b]	382	2 (2−3)	2 (1−3)	2 (1−3)	0.358

Values are presented as number (%) or mean $\pm$ SD.

ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; ATII, angiotensin II; HF, heart failure; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association.

[a]Not normally distributed: minimum−median−maximum.

[b]Median (interquartile 25−75).

[c]pmol/L, reference value <35 pmol/L.

[d]pg/mL, reference value <450 pg/mL.

Subgroup analysis of the primary endpoint with 95% confidence intervals (CIs) was performed using a Cox proportional hazards model.

Results

Of the 382 patients included, 197 were allocated to the intervention group and 185 to the usual-care group. Mean age was 71.5 (32−93) years and 46% were ≥ 75 years old, 59% were male, 65% lived with a partner, and 57% were in functional class II, 40% in class III, and 3% in class IV. Admission for heart failure during 30 days before inclusion occurred in 6.8% of the population and in 16.5% within the 12 weeks before inclusion, without differences between groups.

Mean left ventricular ejection fraction was 0.38, and in 61% it was ≤0.45; 50% had ischaemic heart disease. Study arms were balanced regarding baseline characteristics, except for predominance of atrial fibrillation in the intervention group ($P = 0.007$). Use of heart failure medication was high, as shown in *Table 2*. As seen in *Figure 1*, follow-up was incomplete in 81 (21%)—43 in the usual-care and 38 in the intervention arm—due to death, increasing physical impairment, stress, or losing motivation.

Remote monitoring compliance, programme allocation, and contacts with the heart failure nurse

After the basal set of dialogues during the first 3 months patients were allocated to the best fitting sets: 17 (9%) were re-allocated to the same set, 29 (15%) to sets emphasizing symptoms, 64 (23%) to the education set, and 89 (45%) to a maintenance programme. Sixteen patients (8%) died, dropped out, or did not finish the first set for other reasons.

The overall daily compliance (expressed as the percentage of responses to the total number of daily dialogues for all patients)

with the intervention was 90% (median 92.3, interquartile population range, 84.7−94.9), uncorrected for days in hospital or other reasons for absence. During the first 3 months compliance was 93% and, when repeating the same sets, compliance was 95%. Daily compliance for the sets with emphasis on symptoms and education was 87% and 88%, respectively, and for the maintenance set it was 87%.

Planned and unplanned face to face contacts with the heart failure nurse showed a yearly average of 1.36 (range 0−11) in the intervention group against 1.74 (0−8) in the usual-care group (Mann−Whitney $P < 0.001$). The number of telephone contacts with the nurse was the same in both groups.

Primary endpoint

In *Figure 2A* a trend is presented to a reduced time to first heart failure admission: for the intervention group mean time to first admission was 161 days (range 344, median 170) and for the usual-care group 139 days (range 296, median 126). In the intervention group 18 (9.1%) patients had 24 admissions for heart failure compared with 25 (13.5%) patients with 43 admissions in the usual-care group [difference 4.4 percentage points, Kaplan−Meier $P = 0.151$, hazard ratio (HR) 0.65, 95% CI 0.35−1.17].

Secondary endpoints

The combined endpoint of heart failure admission and all-cause mortality was similar in the intervention and usual-care group (Kaplan−Meier $P = 0.641$, HR 0.89, 95% CI 0.69−1.83) as shown in *Figure 2B*. No difference was found for subgroups. Total number of days in hospital was 1128 vs. 866, respectively (Mann−Whitney $P = 0.338$), and the number of days of admission for heart failure was 253 (22%) and 330 days (38%) for the intervention and usual-care group, respectively (Mann−Whitney $P = 0.156$). *Table 3* shows the number of days of admission for cardiovascular reasons not due to heart failure, 155 (14%) in 26
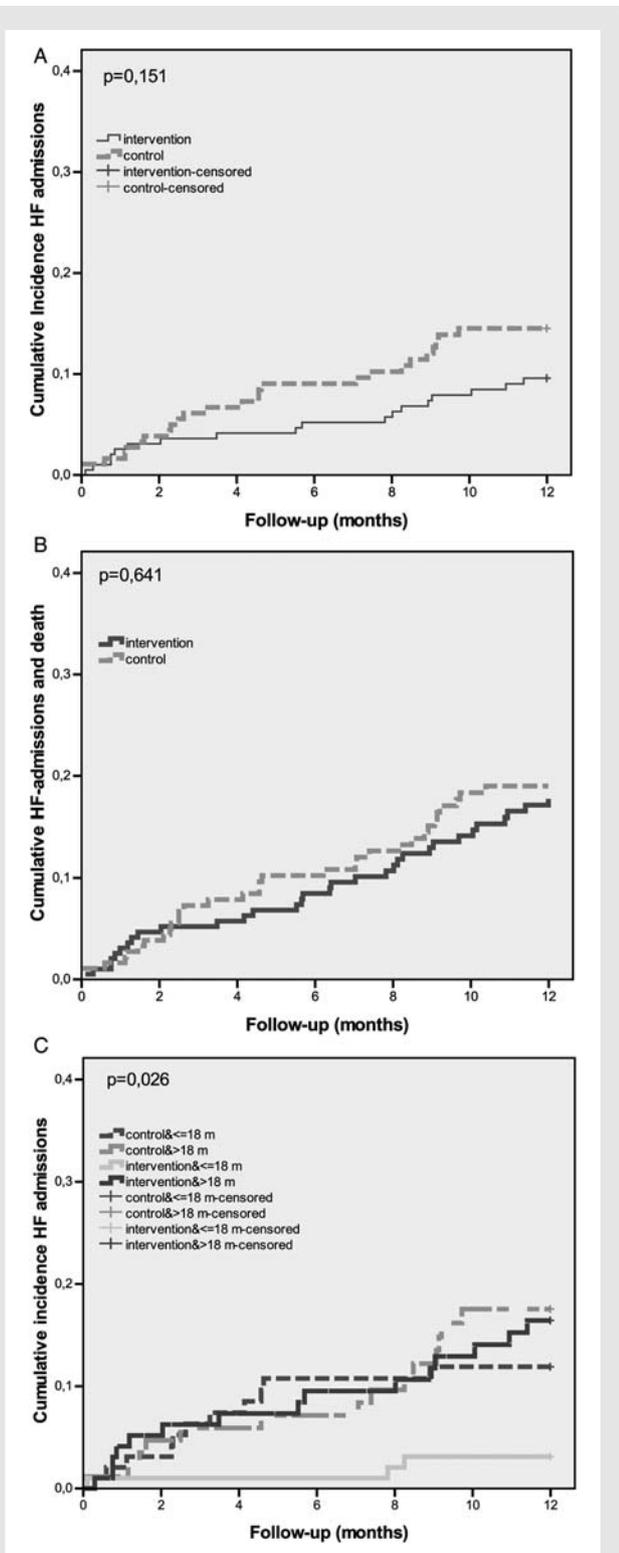
Figure 2 Cumulative incidence of (*A*) time to first hospitalization for heart failure for the intervention and usual-care group, (*B*) time to the combined endpoint of first hospitalization or all-cause death for the intervention and usual-care group, (*C*) time to first hospitalization for both groups and for patients with heart failure duration of more of less than 18 months.

Table 3 Overview of the secondary endpoints, hospitalization and contacts with caregivers

	All patients		P-value
	Intervention (*n* = 197)	**Usual care** (*n* = 185)	
Primary endpoint	18 (9.1)[a]	25 (13.5)	0.15
Secondary endpoints			
All-cause admission rate	117	109	0.35
All-cause admission days	1128	866	0.40
Patients with heart failure admissions	18 (9.1)	25 (13.5)	0.15
One admission	13 (6.5)	14 (7.6)	
Two admissions	4 (2.0)	7 (3.8)	
>2 admissions	1 (0.5)	4 (2.2)	
All admissions for heart failure	24	43	0.18
Total heart failure hospital days	253	330	0.18
Patients with cardiovascular admissions[b]	26 (13.2)	18 (9.7)	0.29
One admission	24 (12.2)	15 (8.1)	
Two admissions	2 (1.0)	1 (0.5)	
>2 admissions		2 (1.1)	
Total cardiovascular hospital days	155	101	0.28
Patients with other causes for admissions	48 (24.8)	35 (18.9)	0.16
One admission	35 (17.1)	30 (16.2)	
Two admissions	11 (5.6)	3 (1.6)	
>2 admissions	2 (1.0)	2 (1.1)	
Total other-cause hospital days	720	435	0.21
Contacts with cardiologist	448 ± 2.29[c]	444 ± 2.40	0.77
Contacts with heart failure nurse	267 ± 1.36	321 ± 1.74	<0.01
Mortality	18 (9.1)	12 (6.5)	0.34
Combined endpoint	32	32	0.64
Total number of days in the study	64 911	59 204	
Mean number of days in the study (per patient)	330	320	

The P-values were obtained by Mann–Whitney test.
[a]Percentage.
[b]Cardiovascular: related to treatment or diagnostics of cardiac disease or heart failure therapy related.
[c]Mean number of contacts

patients vs. 101 (12%) in 18 patients for the intervention and usual-care group, respectively (Mann–Whitney *P* = 0.284). Days of admission for other causes were 720 (64%) in 48 patients and 435 (50%) in 35 patients for the intervention and usual-care group,

Table 4 Univariate and Cox regression analysis of the primary endpoint

	P-value	Hazard ratio	95% CI	
			Lower	Upper
Univariate analysis				
Group (intervention/ usual care)	0.155	0.65	0.35	1.18
Cox regression analysis				
Group (intervention/ usual care)	<0.001	4.96	2.022	12.181
Group × history of HF	0.007	0.98	0.970	0.995
NYHA II	0.020			
NYHA III vs. II	0.006	0.00	<0.001	0.183
NYHA IV vs. II	0.216	0.00	<0.001	49.205
Systolic BP	<0.001	0.94	0.909	0.968
History of HF	0.001	1.02	1.007	1.024
Ischaemia	0.022	2.14	1.113	4.098
Urea	0.001	1.08	1.031	1.122
Haemoglobin	0.004	0.64	0.474	0.867
Heart rate	<0.001	1.05	1.023	1.068
NYHA 2 × systolic BP	0.011			
NYHA III vs. II × systolic BP	0.004	1.06	1.018	1.095
NYHA IV vs. II × systolic BP	0.094	1.08	0.987	1.183

Cox regression analysis was performed to demonstrate the influence of baseline characteristics on admissions for heart failure. Significant interaction effect and their main effect were added into the model with P-value <0.10.
BP, blood pressure; CI, confidence interval; HF, heart failure; NYHA, New York Heart Association.

respectively (Mann–Whitney $P = 0.205$). Re-admissions for heart failure occurred in 5 patients and in 11 patients, respectively (Mann–Whitney $P = 0.097$).

The mean duration per heart failure admission was 9.9 (0–36) days and 8.0 (0–39) days for the intervention and usual-care group, respectively; the duration of non-heart failure admissions was 8.8 (0–112) vs. 7.7 (0–69) days.

Subgroup analysis of the primary endpoint

Cox regression analysis showed an important interaction between group assignment and heart failure duration, $P = 0.007$, odds ratio (OR) = 0.983, 95% CI 0.970–0.995 adjusted for the baseline variables ischaemia, blood urea, haemoglobin level, heart rate, NYHA class, and systolic blood pressure, as shown in Table 4. Subgroup analyses showed that the variables heart failure duration < 18 months (HR 0.26, 95% CI 0.07–0.94, $P = 0.026$), having a pacemaker (HR 0.37, 95% CI 0.15–0.93, $P = 0.030$), and co-habiting (HR 0.42, 95% CI 0.17–1.01, $P = 0.040$) were positive for the telemonitoring arm, as illustrated in Figure 3.

If heart failure duration was ≤18 months, patients had significantly fewer admissions for heart failure (Mann–Whitney

$P = 0.026$) (Figure 2C). Moreover, no patients were re-admitted in the intervention group, compared with 5 patients with 11 re-admissions in the usual care group (Mann–Whitney $P = 0.024$).

Mortality

Eighteen patients (9.1%) died in the intervention group and 12 (6.5%) in the usual-care group (Mann–Whitney $P = 0.34$), due to cardiovascular disease in 11 (61%) compared with 7 (58%), respectively (Mann–Whitney $P = 0.92$). After adjustment for age, NYHA classification, and urea, using Cox regression analysis no statistical difference was found ($P = 0.82$). Mortality was evenly distributed over time.

Discussion

This is the first randomized controlled clinical trial in a heart failure population evaluating a tailored telemonitoring approach aimed at identifying early symptoms and enhancing self-care and treatment adherence through increasing disease-specific knowledge. Nevertheless, due to practical restrictions, tailoring of the telemonitoring was not as advanced as the authors intended; they still talk about "tailoring", while this is a remarkable differentiating feature compared with other telemonitoring systems.

It is concluded that this study resulted in a neutral effect, possibly caused by underpowering of the population on one hand and using medically well treated study groups on the other hand. The latter has limited the room for improvement. Power analysis was based on a 25% admission rate for heart failure.[15] However, this reference population included discharged patients after an admission for heart failure, whereas our patients were recruited at the outpatient clinic, with only 6.8% of patients admitted for heart failure during the 30 days before study enrolment. With respect to the patients in the usual-care group, they mostly were in NYHA class II (57%), medically well treated with 90% on angiotensin-converting enzyme (ACE) inhibitors and 82% on beta-blockers, and undergoing an intensive follow-up at the heart failure outpatient clinic.

Regarding the primary endpoint, a reduced number of hospitalizations for heart failure in contrast to a non-significant increased mortality was found in the intervention group. The higher mortality rate may have influenced the reduction of heart failure admissions. Therefore, a composite endpoint of heart failure admissions and mortality for all causes would have been stronger. Nevertheless, combining heart failure admissions and mortality also resulted in a neutral outcome for the whole study groups, and for the subgroups (data not shown).

Using the distinction between telemonitoring and structured telephone support (STS) as described by Inglis et al.,[16] the TEHAF study belongs to the STS group; however, studies, comparable with our study, with intensified management, were excluded from their systematic review. Inglis et al. found a significantly reduced number of hospitalizations for heart failure ($P < 0.0001$), and all-cause hospitalizations ($P = 0.02$), and a non-significant trend for all-cause mortality ($P = 0.08$). In contrast to these findings, we only found a trend to reduced heart failure hospitalizations and also a high daily adherence to the intervention. The absence of a significant effect on heart failure hospitalizations
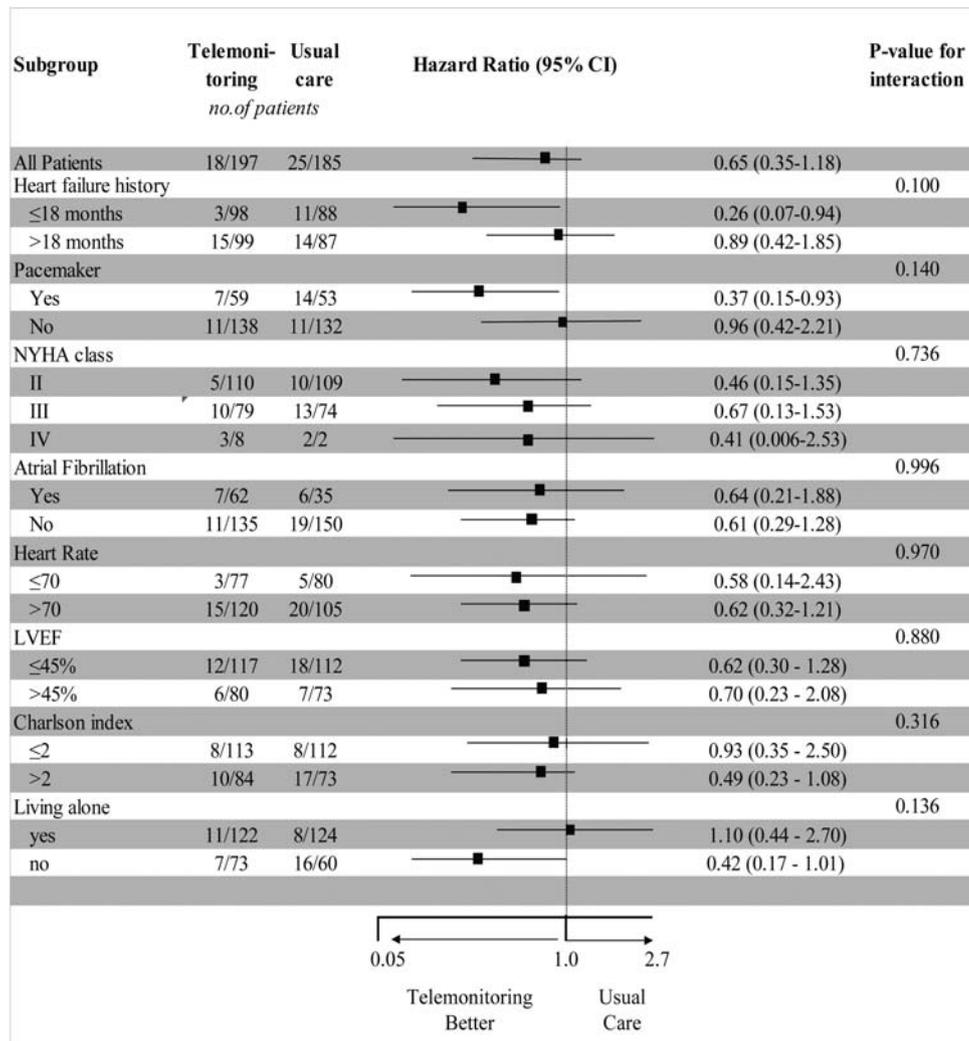
Subgroup	Telemonitoring	Usual care	Hazard Ratio (95% CI)		P-value for interaction
	no. of patients				
All Patients	18/197	25/185		0.65 (0.35-1.18)	
Heart failure history					0.100
≤18 months	3/98	11/88		0.26 (0.07-0.94)	
>18 months	15/99	14/87		0.89 (0.42-1.85)	
Pacemaker					0.140
Yes	7/59	14/53		0.37 (0.15-0.93)	
No	11/138	11/132		0.96 (0.42-2.21)	
NYHA class					0.736
II	5/110	10/109		0.46 (0.15-1.35)	
III	10/79	13/74		0.67 (0.13-1.53)	
IV	3/8	2/2		0.41 (0.006-2.53)	
Atrial Fibrillation					0.996
Yes	7/62	6/35		0.64 (0.21-1.88)	
No	11/135	19/150		0.61 (0.29-1.28)	
Heart Rate					0.970
≤70	3/77	5/80		0.58 (0.14-2.43)	
>70	15/120	20/105		0.62 (0.32-1.21)	
LVEF					0.880
≤45%	12/117	18/112		0.62 (0.30 - 1.28)	
>45%	6/80	7/73		0.70 (0.23 - 2.08)	
Charlson index					0.316
≤2	8/113	8/112		0.93 (0.35 - 2.50)	
>2	10/84	17/73		0.49 (0.23 - 1.08)	
Living alone					0.136
yes	11/122	8/124		1.10 (0.44 - 2.70)	
no	7/73	16/60		0.42 (0.17 - 1.01)	

```
            0.05          1.0        2.7
         Telemonitoring        Usual
            Better             Care
```

Figure 3 Hazard ratio and 95% confidence interval for different subgroups of patients. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

and mortality may have been caused by the very well treated usual-care group, leaving little opportunity for improvement. Follow-up included visits at the outpatient clinic and/or home visits. No distinction was made between these follow-up modalities, although home visits were mostly to more seriously ill patients with a high care consumption, which may have negatively influenced the results. Furthermore, Inglis *et al.* reported two studies with an improved knowledge level, which was comparable with our results, yet a discussion of these results is beyond the scope of this article.

Daily use of the system is a critical factor for success of therapy; therefore, efforts have to be made to increase adherence to the daily system. Notwithstanding the similarity in terms of being categorized as STS, there were some important differences between the TELE-HF and TEHAF studies which may have influenced daily system adherence by patients as well as by caregivers. One important difference was the tailoring of information to patients'

needs and physical stability. For example, patients whose condition was stable received only a few symptomatic questions, whereas questioning about symptoms was intensified in cases of physical instability. Tailoring of information has the potential to involve patients and corresponds most to face to face contacts, giving patients the feeling of being taken seriously and leading to increased patient commitment. Telemonitoring may be considered as a decision-making aid. Decision aids prepare people to be involved in the decision-making process. The ultimate goal of decision aids is to improve decision making in order to reach a high quality decision.[17]

A strategy of applying individualized questions on symptoms at the time of enrolment has been used before,[18] resulting in 98.5% compliance. In addition to the system used in the TELE-HF study, our system delivers education and supports self-management. Curiosity about new information may have triggered an improved daily use of the system by patients. Our impression is

that almost the same not-applicable questions are boring and may lead to non-adherence to the system.

In addition, the system used in this study collected patient information by requiring them to press a button on an appliance, after patients had been read a question on the display, whereas patients in the TELE-HF study had to make a daily toll-free call which may have been experienced as an obstacle to compliance. In contrast to the TELE-HF, no reminders were needed to activate caregivers to review patient information, while reviewing remote information was embedded in the daily organization of nursing care.

Subgroup analysis showed greater effects in patients with a heart failure duration < 18 months, having a pacemaker, and patients not living alone. The effectiveness regarding heart failure duration may be due to a greater willingness to adopt an appropriate lifestyle and to cope effectively with heart failure. Moreover this category mostly has less severe heart failure, and are easier to treat at a distance. Also co-habiting patients seem to benefit more from telemonitoring, possibly caused by encouragement by the partner to use the system. On the other hand, a patient's responsibility for the partner might have been a motive for adherence to the system.

The TEMA-HF[19] study included 160 patients in eight centres, with a mean age of 76 years, and a follow-up time of 6 months. Using a telemonitoring system automatically transferring body weight, blood pressure, and heart rate, a reduced mortality rate ($P < 0.001$), number of re-admissions for heart failure ($P = 0.056$), and number of days to follow-up ($P < 0.02$) were found. Moreover, the system was used as a communication facilitating tool between the heart failure clinic and general practitioners (GPs). Patients were recruited during hospitalization and patients of both groups visited the outpatient clinic 2 weeks after discharge. In addition to this, patients of the telemonitoring group visited the cardiologist after 3 and 6 months, while patients of the usual-care group were followed by their GP. Yet it is unclear whether or not patients in the usual-care group had planned appointments which may have resulted in suboptimal care. This is in contrast to our study where the intervention was superposed on optimal care in both groups, with all patients treated at the heart failure clinic or visited at home. The possible suboptimal care of the usual-care group in the TEMA-HF study may have enhanced the differences between the groups, whereas the optimal treatment for both groups in our study may have mitigated the differences.

No between-group differences for medication were found at baseline in the TEMA-HF study, whereas a significant difference was found to the disadvantage of the usual-care group regarding the use of diuretics, ACE inhibitors, and beta-blockers at the end of the study. This indicates undertreatment of patients in the usual-care group. The combination of suboptimal care and undertreatment in the usual-care group of the TEMA-HF study, in contrast to the well organized care and optimal medication treatment in our study groups, may explain the difference in effects on mortality. Also, patients in the TEMA-HF study were recruited during hospitalization, whereas patients of the TEHAF study were mostly stable as they were recruited at a regular visit to the outpatient clinic. Patients discharged for heart failure are at risk of being re-admitted for heart failure,[20,21] in contrast to stable patients followed at a heart failure clinic. Accordingly, the most benefit to gain in terms of heart failure (re)admissions can be found in recently discharged patients. This discrepancy in study populations may explain the difference in the reduced number of heart failure admissions between the studies. However, subanalysis in our study found differences between groups depending on their heart failure duration, whereas the TEMA-HF study described no subgroup analysis. It would be interesting to know whether the results of the TEMA-HF study could be attributed to the automated data transfer only, to the improved communication between caregivers, or to both. However, the introduction of a telemonitoring application to improve communication between caregivers is new and challenging, and the positive results and experiences create opportunities where cooperation between caregivers is needed. Another method of remote monitoring is the use of an implantable diagnostic tool to measure intrathoracic impedance. Van Veldhuizen et al.[22] reported on a clinical trial comparing one study group with access to all device-based diagnostic information with a group without this information available. The primary endpoint was heart failure hospitalizations and all-cause mortality. A total of 168 participated in the intervention and 167 in the control arm. Patient characteristics were comparable with those of our study regarding NYHA classification, medication prescription, and type of heart failure, yet differed in terms of left ventricular ejection fraction (25% vs. 35%), mean age (64 vs. 72 years), and gender (male 86% vs. 59%). A remarkable feature of the DOT-HF study is the high number of admissions for heart failure (96) as well as for other cardiovascular reasons (189), which is in contrast to our study, whereas mortality was comparable. The high number of hospitalizations in the treatment arm was unexpected, as using intrathoracic impedance previously has been shown to reduce hospital admissions.[23–25] Although early signs and symptoms are reported to be unspecific,[26] impedance monitoring also did not succeed in preventing admissions for heart failure (HR 1.79). Remarkable and rather distressing is the high number of patients in the study arm admitted with signs and symptoms of heart failure yet without an Optivol alert, indicating signs and symptoms to be more reliable than impedance monitoring. The large number of outpatient unplanned visits in the DOT-HF study is also in contrast to our study which showed a significant reduction in face to face contacts with the nurse.

Of note in the DOT-HF study is the contrast between the high number of alerts requiring physical examination on the one hand, and the number of patients admitted without Optivol alerts on the other hand. Those findings suggest that monitoring intrathoracic impedance is unreliable at the moment and is not ready (yet) for implementation in daily practice. The authors conclude that further studies are needed to examine the place of this feature; a suggestion may be to collect patient data regarding signs and symptoms, while the current study has proven that evaluation is useful both to guide patients at a distance resulting in fewer heart failure hospitalizations and contacts with caregivers, in contrast to the DOT-HF study underestimating signs and symptoms. The combination of data collection of impedance and symptoms may provide more insight into the relationship between both which probably will improve the usefulness of this feature.

Angermann et al.[27] described their experiences with the INH study with an intervention existing of a combination of different actions such as intensive telephone contacts between the specialist

nurse and the patient with structured monitoring of symptoms, medication, mood, and well-being; up-titration of medication; availability of blood pressure and weight; and the need for adjusted specialist care. The study population consisted of patients with systolic heart failure; 352 in the intervention (HNC) and 363 in the control (UC) arm. No difference was found regarding the primary endpoint of time to death or re-hospitalization; however, patients in the HNC arm were more frequently re-admitted, whereas in the UC arm more patients died, which was in contrast to our study. They also found surrogates for improved well-being in the HNC group, yet it is not clear which part of the intervention is responsible for that finding. The high number (37%) of questions related to non-cardiac problems was remarkable, again demonstrating the complexity of care for heart failure patients. In their discussion, Angermann *et al.* state that comprehensive care models have to integrate specific surveillance for the complex facets of heart failure and physical problems of multimorbidity and old age, and we agree with this. However, it has to be determined whether for patients frequently needing more attention for non-cardiac problems a generalist nurse preferably should supervise them rather than a specialized nurse. The number of non-cardiac problems probably is even higher in the group of patients suffering from heart failure with preserved systolic function, while those patients mostly are older; because only patients with systolic heart failure were included, information about the effect on this important heart failure category is missing. Involving patients with diastolic heart failure would probably have strengthened their findings. Regarding the high number of patients who withdrew from the intervention it would be interesting to know why they withdrew, yet unfortunately the authors gave no explanation of this finding.

The 21% of patients not completing the 1 year follow-up was comparable with a recently published study[6] and is expected, given their limited general condition and older age. The drop-out rate was higher in the usual-care group, mainly due to loss of interest and loss to follow-up.

Similar to the HOME-HF study,[28] a reduction in face to face contacts was found. While our contacts concern the heart failure nurse, it remains unclear which contacts were reduced in the HOME-HF-study as the authors were referring to secondary outpatient visits.

No significant difference was found for mortality, suggesting there was no negative effect of the intervention and of the reduced number of face to face contacts. This finding and the decreased number of heart failure admissions suggest the intervention to be cost-effective.

Regarding the different programmes used in this study, their specific value cannot be commented on, as this was not part of the study.

Limitations

This study was slightly underpowered due to a power calculation based on a recently admitted heart failure population whereas our population was recruited from regular outpatient visits. A combined endpoint of heart failure hospitalizations and mortality would have been appropriate. No subgroups were pre-specified, therefore the results of the subgroup analysis have to be considered as hypothesis generating, in future research. There was a

slightly unequal distribution over the study arms, although this had no effect on baseline characteristics and clinical descriptors. All-comer outpatients with stable heart failure were enrolled, resulting in a heterogeneous mix of differences in hospitalization rates, heart failure severity, stages of heart failure, and co-morbidities. However, the study groups were well balanced concerning these items. In addition, recruitment of a real-life population strengthens the external validity of our findings. Not all participants completed the full follow-up, mostly due to age and the disease severity typical for the study population.

Conclusion

No significant differences were found regarding the primary endpoint, most probably caused by a relative underpowering of the population combined with well treated study groups. However, telemonitoring tends to reduce heart failure (re)admissions and significantly decreases contacts with specialized nurses. Further research is required to investigate telemonitoring in pre-specified subgroups, and the match between the system and the patient.

These data about stable clinic patients may provide information for power analysis in future studies.

Appendix: Members of the TEHAF study group

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