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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

John G. F. Cleland, MD,* Amala A. Louis, MD,* Alan S. Rigby, PHD,* Uwe Janssens, MD,† Aggie H. M. M. Balk, MD,‡ on behalf of the TEN-HMS Investigators

Kingston Upon Hull, United Kingdom; Aachen, Germany; and Rotterdam, the Netherlands

OBJECTIVES We sought to identify whether home telemonitoring (HTM) improves outcomes compared with nurse telephone support (NTS) and usual care (UC) for patients with heart failure who are at high risk of hospitalization or death.

BACKGROUND Heart failure is associated with a high rate of hospitalization and poor prognosis. Telemonitoring could help implement and maintain effective therapy and detect worsening heart failure and its cause promptly to prevent medical crises.

METHODS Patients with a recent admission for heart failure and left ventricular ejection fraction (LVEF) <40% were assigned randomly to HTM, NTS, or UC in a 2:2:1 ratio. HTM consisted of twice-daily patient self-measurement of weight, blood pressure, heart rate, and rhythm with automated devices linked to a cardiology center. The NTS consisted of specialist nurses who were available to patients by telephone. Primary care physicians delivered UC. The primary end point was days dead or hospitalized with NTS versus HTM at 240 days.

RESULTS Of 426 patients randomly assigned, 48% were aged >70 years, mean LVEF was 25% (SD, 8) and median plasma N-terminal pro-brain natriuretic peptide was 3,070 pg/ml (interquartile range 1,285 to 6,749 pg/ml). During 240 days of follow-up, 19.5%, 15.9%, and 12.7% of days were lost as the result of death or hospitalization for UC, NTS, and HTM, respectively (no significant difference). The number of admissions and mortality were similar among patients randomly assigned to NTS or HTM, but the mean duration of admissions was reduced by 6 days (95% confidence interval 1 to 11) with HTM. Patients randomly assigned to receive UC had higher one-year mortality (45%) than patients assigned to receive NTS (27%) or HTM (29%) ($p = 0.032$).

CONCLUSIONS Further investigation and refinement of the application of HTM are warranted because it may be a valuable role for the management of selected patients with heart failure. (J Am Coll Cardiol 2005;45:1654–64) © 2005 by the American College of Cardiology Foundation

Epidemiologic studies suggest that one in six members of the population will develop heart failure (1,2). Heart failure is one of the most common medical reasons for admission to the hospital and has a three-year mortality rate of approximately 60% (3,4). After a person is admitted to the hospital with heart failure, there is a one in four chance of that patient's rehospitalization or death within 12 weeks (5).

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Effective treatment is available for heart failure due to left ventricular (LV) systolic dysfunction (6). Unfortunately, because of inadequate organization of care, effective pharmacologic treatment often is not given and, when it is, often at doses lower than those shown to be effective (5,7). There is growing evidence that improved organization of heart failure care, as for other malignant diseases, can have a major impact on hospitalization and/or death (8–12). However, relative to the number of patients affected, there is a lack of healthcare staff able to provide expert management for heart failure. Novel methods for the delivery of quality healthcare could increase the effectiveness of management while containing costs and using scarce human resources to maximum effect.

Interest in telemedicine as a way of providing care has been stimulated by the rising costs of hospital treatment, rapid advances in technology, and the wider availability of low-cost, patient-friendly equipment (13,14). Home telemonitoring (HTM) allows the evaluation of patients' vital

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
HTM	= home telemonitoring
LV	= left ventricular
NT-proBNP	= N-terminal pro-brain natriuretic peptide
NTS	= nurse telephone support
NYHA	= New York Heart Association
TEN-HMS	= The Trans-European Network–Home-Care Management System
UC	= usual care
WHARF	= Weight Monitoring in Heart Failure

signs once or more per day and provides diagnostic information that can be transmitted to health professionals. It has the potential to involve patients more in their own care, assist the titration of medications, improve compliance, and help providers identify early signs of worsening heart failure and its precipitating factors. Home telemonitoring also may assist with care at home or early discharge planning, thereby reducing admissions, hospital days, and rates of mortality. The purpose of the Trans-European Network–Home-Care Management System (TENS-HMS) study was to address some of these issues.

METHODS

Centers and patients. Hospitals that did not already have a comprehensive heart failure management organization in place were selected, although most had one or more specialist nurses and doctors interested in the management of heart failure. Twelve main and four satellite hospitals in Germany, the Netherlands, and the United Kingdom were identified. Each hospital provided a secondary care function to their local community from which patients were recruited.

Patients who were ready for or recently discharged after an admission for worsening heart failure were evaluated for inclusion provided their primary care physician agreed. To be included, patients had to have a hospital admission due to or complicated by worsening heart failure lasting >48 h within the last six weeks; to have persisting symptoms of heart failure, a LV ejection fraction <40%, an LV end-diastolic dimension >30 mm/m (height); and to be receiving furosemide at a dose ≥40 mg/day or equivalent (e.g., ≥1 mg of bumetanide or ≥10 mg of torasemide). In addition to these criteria, patients had to have at least one of the following markers of a further increase in risk: an unplanned cardiovascular admission lasting >48 h within the previous 2 years, an LV ejection fraction <25%, or treatment with furosemide at a dose of ≥100 mg/day or equivalent. Patients who were younger than 18 years of age; who were deemed unable to comply with home telemonitoring; or who were awaiting revascularization, cardiac resynchronization, or heart transplantation were excluded. The study adhered to local and international guidelines for good clinical practice and was approved by relevant ethical committees for each participating hospital. Written informed consent was obtained from all patients.

Methods. Baseline demographic and social details, clinical history, medication, New York Heart Association (NYHA) functional classification, weight, and physical signs were recorded, and a blood sample was taken for the measurement of hemoglobin, electrolytes, urea, creatinine, and N-terminal pro-brain natriuretic peptide (NT-proBNP; Roche Elecsys proBNP assay, Mannheim, Germany).

Patients were then assigned randomly to receive HTM, nurse telephone support (NTS), or usual care (UC). The main comparison of interest was that between NTS and HTM and, accordingly, twice as many patients were as-

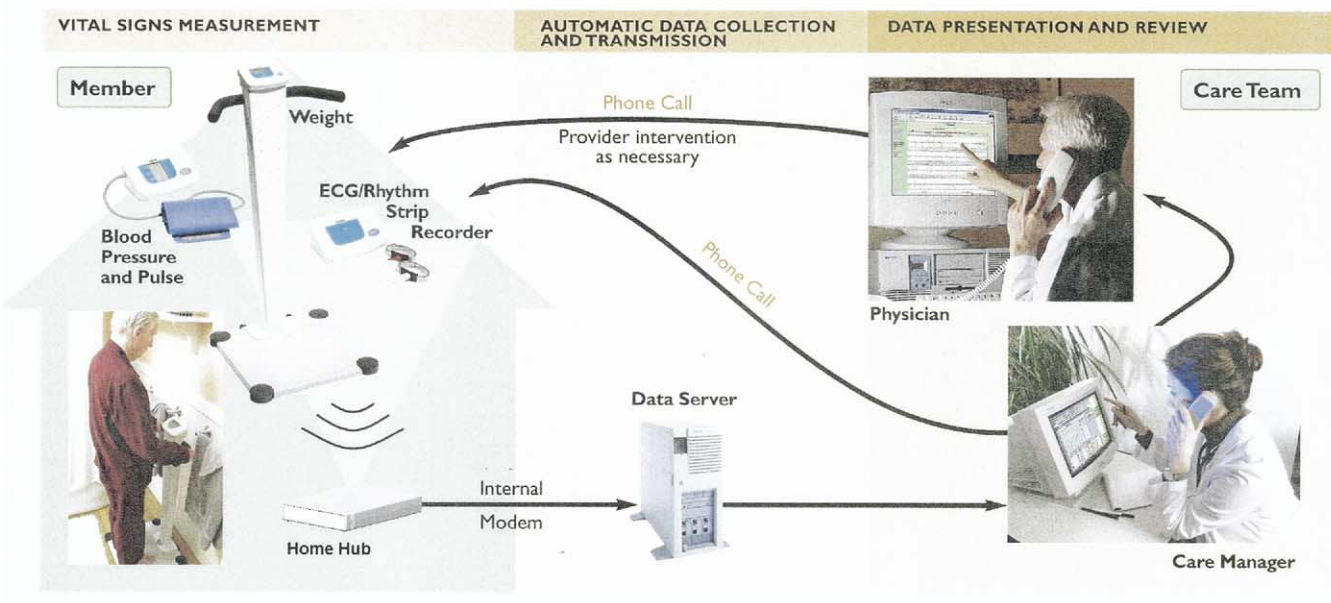

Figure 1. Diagrammatic representation of the telemonitoring system used in the trial. ECG = electrocardiogram.

signed randomly to these groups. The UC group was used as a reference to ascertain whether either HTM or NTS had changed outcome.

After acquiring consent, patients' baseline data were recorded and sent to an independent statistical group (i.e., Institute for Medical Informatics and Biostatistics, Basel). Random permuted blocks for each center were used to allocate patients to treatment groups. The block size was kept confidential and was varied to avoid investigators predicting which management-group would be the next to be allocated.

All patients were given an individualized written management plan by the investigator that described what pharmacologic treatment they should receive, in what order, and how it should be monitored. All patients required a loop diuretic according to the study entry criteria. The management plan focused on treatment of LV systolic dysfunction with appropriate doses of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers and, if severe symptoms persisted, spironolactone according to regional guidelines (15). Digoxin and anticoagulants were recommended for patients in atrial fibrillation. Patients who could not tolerate or who had contraindications to the aforementioned medication were permitted in the study provided an explanation was given.

For patients assigned randomly to UC, the patient management plan was sent to the patient's primary care physician, who was asked to implement it. Where the usual organization of care involved nurse specialist titration of drugs, this was allowed. Patients were assessed at a research clinic every four months to assess intervening history, symptoms and signs, renal function, and serum electrolytes. Contact with the research team was discouraged between visits.

Patients assigned randomly to receive NTS also were managed as described for UC except they were contacted by telephone each month by a heart failure specialist nurse to assess their symptoms and current medication. The nurse could proffer advice to the patient at this time and provide feedback to the primary care provider. Patients also were told that they could contact the study nurse by telephone at any time, either directly or by leaving a message on a telephone-answering machine. However, should an out-of-hours emergency arise, they were told to contact their primary care doctor or the ambulance service.

Patients assigned randomly to HTM received instructions on how to use the telemonitoring equipment, and nurse telephone support was offered as for the NTS group. As soon as possible after randomization (median 12 days; upper quartile 24 days), a service engineer visited the patient's home to install the equipment, which consisted of low-profile, electronic, weighing scales, an automated sphygmomanometer, and a single-lead electrocardiogram using wrist-band electrodes (Fig. 1). Each device contained a short-range radio-transmitter that allowed it to communicate automatically with a hub connected to the patient's conventional telephone line and, thereby, automatically to a central web server and then via secure Intranet connections to a workstation at each investigator site. Data were encrypted during transmission to ensure patient confidentiality. Patients were asked to make a set of measurements every day before breakfast and before their evening meal, after

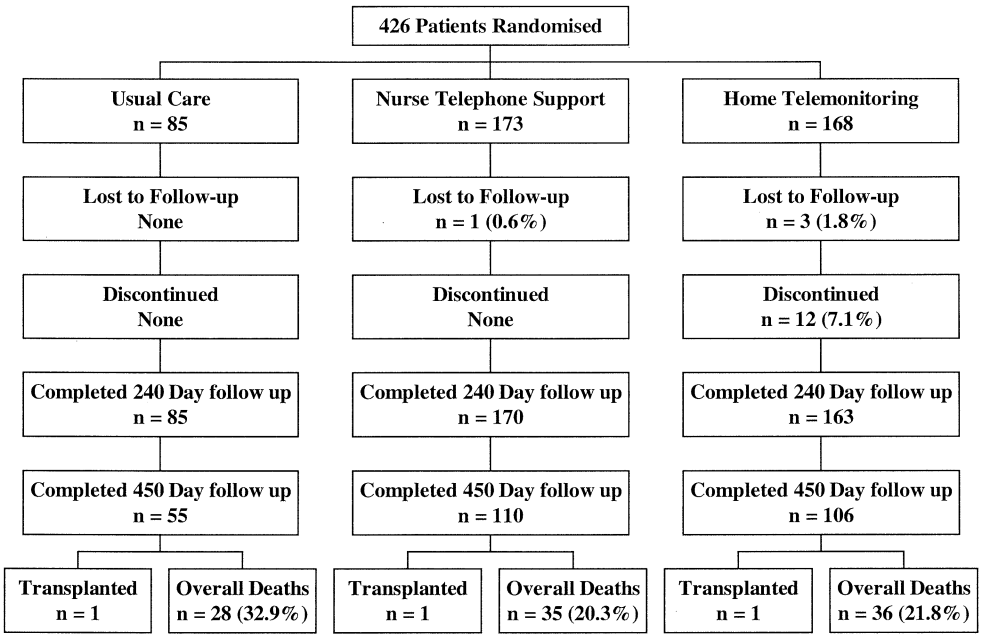

Figure 2. Consort diagram showing distribution, follow-up, and outcome of patients.

Table 1. Baseline Characteristics

Variable	Usual Care	Nurse Telephone Support	Home Telemonitoring
Number randomly assigned	85	173	168
Mean age, yrs (SD)	68 (10)	67 (11)	67 (13)
% patients age ≥70 yrs	49	47	54
Women (%)	18	28	20
Lives alone	22 (26%)	49 (28%)	40 (24%)
Lives with partner or friend	62 (73%)	123 (71%)	128 (76%)
Primary cause of heart failure			
Coronary disease	58 (68%)	94 (54%)	102 (61%)
Hypertension	4 (5%)	16 (9%)	7 (4%)
Idiopathic dilated cardiomyopathy	14 (17%)	37 (21%)	44 (26%)
Alcohol-related	3 (4%)	5 (3%)	3 (2%)
Valve-related	4 (5%)	16 (9%)	8 (5%)
Other	2 (2%)	4 (2%)	4 (2%)
Comorbidities			
Previous myocardial infarction	57 (67%)	90 (52%)	94 (56%)
Valve disease/mitral regurgitation	31 (36%)/28 (33%)	61 (35%)/52 (30%)	64 (38%)/58 (35%)
Chronic or paroxysmal atrial fibrillation	33 (39%)	80 (46%)	79 (47%)
Hypertension	34 (40%)	92 (53%)	74 (44%)
Stroke, any	7 (8%)	17 (10%)	15 (9%)
Chronic lung disease	25 (29%)	38 (22%)	40 (24%)
Diabetes, any	30 (35%)	60 (35%)	59 (35%)
Systolic blood pressure (mm Hg)	115 (19)	116 (21)	112 (18)
Diastolic blood pressure (mm Hg)	69 (12)	69 (11)	69 (11)
Weight (kg)	79.9 (17.2)	74.9 (16.1)	76.9 (17.1)
Body mass index	27.0 (5.0)	25.8 (4.5)	26.1 (4.9)
Investigations			
Hemoglobin (g/dl)	13.2 (1.9)	13.3 (2.4)	13.0 (1.9)
Serum sodium (mmol/l)	137 (4)	138 (5)	137 (5)
Serum creatinine (μmol/l)	140 (50)	136 (56)	133 (50)
Mean LVEF (%)	24 (8)	25 (8)	25 (8)
% with LVEF <25%	57	50	48
NT proBNP (pg/ml), median [IQR]	2,309 [1,057 to 6,935]	2,909 [1,116 to 6,140]	3,873 [1,607 to 7,518]
Mean dose of furosemide or equivalent, mg (SD)	104 (92)	112 (85)	112 (93)

IRQ = interquartile range; LVEF = left ventricular ejection fraction.

Table 2. NYHA Functional Class Before and After Randomization

	Worst State in Last Month	At Randomization	120-Day Follow-Up*	240-Day Follow-Up*
Usual care				
NYHA I	5 (6%)	14 (18%)	14 (18%)	13 (17%)
NYHA II	10 (13%)	28 (36%)	27 (35%)	20 (26%)
NYHA III	23 (30%)	33 (42%)	16 (21%)	15 (19%)
NYHA IV	40 (51%)	3 (4%)	4 (5%)	8 (10%)
Dead			17 (22%)	22 (28%)
Nurse telephone support				
NYHA I	4 (3%)	28 (18%)	34 (21%)	40 (25%)
NYHA II	23 (15%)	70 (44%)	62 (39%)	47 (30%)
NYHA III	35 (22%)	47 (30%)	33 (21%)	34 (21%)
NYHA IV	97 (61%)	14 (9%)	9 (6%)	7 (4%)
Dead			21 (13%)	31 (19%)
Home telemonitoring				
NYHA I	7 (5%)	34 (22%)	35 (23%)	36 (24%)
NYHA II	24 (16%)	71 (46%)	71 (46%)	53 (35%)
NYHA III	28 (18%)	35 (23%)	27 (18%)	27 (18%)
NYHA IV	94 (61%)	13 (8%)	5 (3%)	9 (6%)
Dead			15 (10%)	28 (17%)

A report on NYHA functional class was missing at one or more time points in 7 patients randomly assigned to usual care, 14 patients to nurse telephone support, and 15 patients to home telemonitoring. Percentages shown are percentage of those in whom data on NYHA were adequately reported. *Data for evaluation closest to 120 and 240 days were used; hence, numbers of deaths differ slightly from those shown in Table 4, in which the data for 240 days precisely are shown.

NYHA = New York Heart Association.

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Table 3. Medication Use According to the Patient's Management Plan (PMP)

	Baseline					
	UC		NTS		HTM	
	n Treated	% Treated	n Treated	% Treated	n Treated	% Treated
Deaths	N/A	0.0%	N/A	0.0%	N/A	0.0%
Patients alive and with available management plan	81	100%	163	100%	160	100%
ACE inhibitors and ARBs						
Intention to treat with ACE inhibitor	67		141		139	
Actually receiving ACE inhibitor (and % intended by PMP)	61	91%	137	97%	130	94%
Intention to treat with ARB inhibitor	12		17		8	
Actually receiving ARB (and % intended by PMP)	6	50%	9	53%	2	25%
Beta-blockers						
Intention to treat with beta-blocker	57		109		101	
Actually receiving beta-blocker (and % intended by PMP)	44	77%	86	79%	87	86%
Spironolactone						
Intention to treat with spironolactone	50		114		101	
Actually receiving spironolactone (and % intended by PMP)	37	74%	91	80%	81	80%

*p = 0.0002 for HTM vs. NTS; †p = 0.0166 for HTM vs. UC (p = 0.0014 for chi-squared in 3-way comparison); ‡p = 0.0007 for HTM vs. NTS; §p = 0.0392 for HTM vs. UC (p = 0.0040 for chi-squared in 3-way comparison); ‖p = 0.0097 for HTM vs. NTS (p = 0.0354 for chi-squared in 3-way comparison); ¶data for evaluation closest to 120 and 240 days were used, hence numbers of deaths differ slightly from those shown in Table 4, in which the data for 240 days precisely are shown.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; HTM = home telemonitoring; NTS = nurse telephone support; PMP = patient management plan; UC = usual care.

emptying their bladders, while wearing light clothing, no shoes, and before the next dose of medication. Thus, the patient's weight, blood pressure, heart rate, and rhythm were monitored twice daily. Values greater than or less than preset limits were notified automatically to the study nurses, who then reviewed the information and took action either directly for any short-term advice or through the primary care physician if long-term changes in therapy were required. Nurses also could scan patient data manually to identify any trends that they considered as requiring action. Study personnel were primarily responsible for implementation of the management plan in patients assigned randomly to HTM. The primary care physician and the investigator were kept informed of all contacts.

Guidelines for the management of a number of common scenarios, depending on the stability of the patients' symptoms and current treatment, were developed by the steering group. A weight change of >2 kg, a resting heart rate <50 beats/min or >80 beats/min, new-onset sustained arrhythmia, or a systolic blood pressure <90 mm Hg or >140 mm Hg were considered an indication for close review of the patient's management. During titration of beta-blockers, a heart rate <65 beats/min was an indication to delay further increases in dose.

Outcome measures. The primary outcome was days lost because of death or hospitalization in acute medical/surgical beds for any reason during 450 days, and the primary comparison of interest was between patients assigned randomly to NTS and HTM. The assumption was that the primary effect of HTM, compared with NTS, would be to reduce bed-days occupancy. Because this outcome is determined partly by the duration of follow-up and by mortality, a fixed duration of follow-up was incorporated into the definition. After an interim analysis (see "Interim analysis"), the duration of follow-up was reduced to 240 days. All-cause mortality, symptoms, and optimization of medication were secondary outcomes. Investigators were asked to classify hospitalizations as due to heart failure, other cardiovascular, or noncardiovascular. Deaths were classified as sudden, due to circulatory failure, or due to other causes.

Sample size. We assumed that HTM would not alter survival, but we included a survival component in the primary end point because the number of days alive is a major determinant of days in hospital. We estimated that mortality would be 2% per month for the first 3 months, 1.5% per month for the next 3 months, and 1% per month thereafter (4). We assumed that the NTS groups would spend an average of 10% of days-alive (41 days) in hospital (4) and that this would be reduced to 6% (25 days) by HTM. In other words, days lost to death or hospitalization would be reduced from 80 days to 63 days during 450 days follow-up, representing 17.8% and 14.0% of days exposure, respectively. We also expected a highly skewed distribution in the primary outcome, with approximately 25% of patients in the control group surviving until the end of the study without any hospital admission. Using a Wilcoxon (Mann-Whitney) rank-sum test, a study with 145 patients in each of the two arms of primary interest was calculated to have 80% power to show significance at p = 0.01 using a two-sided test. A total of 195 patients per arm would provide 90% power. The power calculations appeared robust to a 10% to 20% rate of discontinuation of HTM. Accord-

120 Days Follow-Up¶						240 Days Follow-Up¶					
UC		NTS		HTM		UC		NTS		HTM	
n Treated	% Treated	n Treated	% Treated	n Treated	% Treated	n Treated	% Treated	n Treated	% Treated	n Treated	% Treated
13	18%	18	12%	13	9%	19	26%	27	18%	27	18%
60	82%	134	88%	133	91%	55	74%	125	82%	120	82%
54		118		121		50		112		109	
42	78%	103	87%	116	96%*†	40	80%	98	88%	93	85%
8		15		8		7		15		8	
6	75%	10	67%	3	38%	4	57%	8	53%	4	50%
47		91		90		44		84		82	
34	72%	76	84%	84	93%‡§	34	77%	74	88%	75	92%
38		97		85		36		93		79	
27	71%	62	64%	69	81%‖	27	75%	66	71%	63	80%

ingly, we planned to assign 200 patients randomly to HTM, 200 to NTS, and 100 to UC.

Statistical analysis. Analyses were conducted by intention-to-treat. Baseline characteristics were expressed as mean and standard deviation or median and interquartile range. Treatment groups were compared using a two-sample Wilcoxon test. Outcome measures were expressed as differences between means with 95% confidence intervals, calculated using the Scheffe's multiple comparison procedure. Categorical variables were analyzed using the chi-square test. Continuous outcome variables were not normally distributed and, therefore, the Kruskal-Wallis test was used.

For the survival distribution and statistical comparison, the Kaplan-Meier estimation method with 95% confidence level for survivor function was used. An exploratory multivariate Cox regression analysis was performed that included the following covariates: assigned group, age, NT proBNP, body mass index, systolic and diastolic blood pressure, hemoglobin, sodium, urea, creatinine, NYHA functional classification, loop and potassium-sparing diuretics, ACE inhibitors, and beta-blockers. Covariates were entered into the model if the p value was <0.1. The final model was analyzed using the selected covariate and the variable treatment group and applying Cox regression with stepwise forward selection (entry p value 0.05).

Predefined subgroup analyses included age (lower two terciles vs. upper tercile), gender, etiology of heart failure (ischemic heart disease vs. other), LV ejection fraction (lower two terciles vs. upper), dose of loop diuretic (40 mg vs. >40 mg/day), and plasma concentration of NT-proBNP (lower tercile vs. upper two terciles). The statistical analysis was conducted using the SAS System version 8.2 (SAS Institute, Cary, North Carolina).

Interim analysis. An interim analysis was conducted by the independent statistical group (Institute for Medical Informatics and Biostatistics) after 426 patients had been recruited. They requested that recruitment of patients should stop and the trial brought to a close because of a large difference in mortality rates between the UC care group and those assigned randomly to NTS or HTM and because it was unlikely that the primary end point would be reached. After examining the mortality data, the steering committee agreed to close the study to recruitment, inform the investigators of the mortality difference, but continue follow-up until October 2002 to allow an evaluation of days lost to death or hospitalization over the course of 240 days in almost all patients. This point became the revised primary outcome measure.

RESULTS

Between August 2000 and March 2002, 426 patients were assigned randomly, of whom 4 were lost to follow-up and 12 declined to comply with regular telemonitoring over a median follow-up of 484 (interquartile range, 317 to 622) days (Fig. 2). A total of 81% of patients assigned randomly to HTM had >80% compliance with at least one daily measurement (weight or blood pressure), and 55% had >80% compliance with twice daily measurements. A total of 296 patients died or had at least one day in hospital. Four patients had <240 days of follow-up (2 in NTS and 2 in HTM).

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Table 4. Primary Outcome Measure and its Components at 240-Day Follow-Up

240-Day Follow-Up	UC	NTS	HTM	HTM vs. NTS	HTM vs. UC	NTS vs. UC
Number of patients	85	170	163	Difference between means and 95% confidence interval		
Potential days	19,974	40,192	38,539		Not analyzed	
Patients hospitalized	46 (54%)	85 (49%)	80 (47%)		Not analyzed	
Number of hospitalizations	69	144	155		Not analyzed	
Days in hospital	813 (4.1%)	2,514 (6.3%)	1,779 (4.6%)	−4 (−10 to +2)	−1 (−9 to +6)	+5 (−2 to +13)
Duration per admission (median IQR)	7 (4 to 12)	12 (5 to 21)	9 (4 to 15)	−6 (−11 to −1)	0 (−7 to +6)	+6 (−1 to +12)
Patients hospitalized for heart failure	24 (28%)	34 (20%)	40 (25%)		Not analyzed	
Heart failure hospitalizations	33	47	67		Not analyzed	
Other cardiovascular hospitalizations	23	58	42		Not analyzed	
Noncardiovascular hospitalizations	13	39	46		Not analyzed	
Days in hospital for heart failure	512 (2.6%)	1115 (2.8%)	971 (2.5%)	−1 (−5 to +4)	0 (−5 to +5)	−1 (−6 to +5)
Duration per heart failure admission (median IQR)	11 (6 to 20)	15 (7 to 29)	11 (6 to 19)	−9 (−20 to +2)	−1 (−13 to +11)	+8 (−5 to +21)
Deaths	20 (24%)	27 (16%)	28 (17%)		Not analyzed	
Circulatory failure	14	21	17		Not analyzed	
Sudden death	4	5	9		Not analyzed	
Other	2	1	2		Not analyzed	
Days lost due to death	3,072 (15.4%)	3,875 (9.6%)	3,119 (8.1%)	−4 (−20 to +12)	−17 (−36 to +2)	−13 (−33 to +6)
Patients dead or with at least one hospitalization	48 (56%)	92 (54%)	83 (51%)		Not analyzed	
Days dead or hospitalized	3,885 (19.5%)	6,389 (15.9%)	4,898 (12.7%)	−8 (−25 to +10)	−16 (−37 to +6)	−8 (−29 to +13)

HTM = home telemonitoring; IQR = interquartile range; NTS = nurse telephone support; UC = usual care.

The baseline characteristics of this population and the numbers assigned to each group are shown in Tables 1 to 3. The median duration of heart failure was 2.2 (range 0.2 to 5.2) years and, excluding the index admission, patients had had an average of two heart failure-related admissions in the previous year. Most patients had experienced an episode of NYHA class IV heart failure in the previous month (Table 2), although 62% reported well-controlled symptoms (NYHA functional class I/II) at the time of assignment. However, other variables indicated a poor prognosis (16). For instance, 48% of patients were aged >70 years, ischemic heart disease was common, LV ejection fraction was severely depressed, mean systolic blood pressure was low, and diuretic doses, mean serum creatinine, and plasma NT-proBNP were high. Patients were managed intensively even before randomization (Table 3).

Over the course of 240 days, fewer days were lost to death or hospitalization among patients who were assigned randomly to HTM compared with NTS, but this number did not achieve statistical significance (Table 4). A total of 71% of hospitalizations were cardiovascular (262 of 368) but only 40% (147) were related to heart failure. Home telemonitoring was associated with a trend to more hospital admissions with heart failure but a significant reduction in the average duration of admissions compared with NTS. Overall, there was a trend to a reduction in days in hospital with HTM compared with NTS (10.9 days vs. 14.8 days). Home telemonitoring reduced days in hospital for heart failure and for other causes similarly. Patients assigned to UC fared worst, predominantly because of poorer survival. A total of 271 patients (64%) were followed for 450 days. No significant differences were observed between HTM and NTS at 450 days in primary or secondary outcomes (Table 5). Compared with those in UC, patients assigned to HTM or NTS had a significantly lower rate of mortality and consequently lost fewer days to death or hospitalization.

The study was not adequately powered for a robust subgroup analysis. Exploratory analyses did not identify any specific subgroup that obtained significantly greater benefit from HTM compared with NTS for the primary end point. Patients assigned randomly to receive UC had a significantly higher all-cause mortality than patients assigned to NTS or HTM (Fig. 3). Variables carrying independent prognostic value in the multiple covariate Cox regression analysis are shown in Tables 6 and 7. In this model, increments in NT-proBNP (per tercile) had the strongest association with adverse outcome (Fig. 4), whereas assignment to receive UC was independently associated with an adverse prognosis.

The NYHA functional class was similar among surviving patients in the three groups at 120 days and 240 days (Table 2). At 120 days, patients assigned randomly to receive HTM were more likely to receive ACE inhibitors, beta-blockers, and spironolactone according to their management plan than those assigned to NTS and more likely to receive ACE inhibitors and beta-blockers than those assigned to UC (Table 3). No significant differences were found between NTS and UC with regards to the uptake of treatment. By 240 days, these differences were no longer significant.

Data on patient contacts other than hospitalization were collected by monthly review in the NTS and HTM groups but only every four months in the UC group (Table 8). This difference may have led to under-reporting of contacts in the latter group. The NTS and HTM groups were associated with a substantial and similar increase in reported patient-contacts, including emergency room, home and office visits,

Table 5. Primary Outcome Measure and its Components at 450-Day Follow-Up

450-Day Follow-Up	UC	NTS	HTM	HTM vs. NTS	HTM vs. UC	NTS vs. UC
Number of patients	55	110	106	Difference between means and 95% confidence interval		
Potential days	24,750	49,500	47,700		Not analyzed	
Patients hospitalized	40 (73%)	73 (66%)	75 (71%)		Not analyzed	
Number of hospitalizations	85	151	159		Not analyzed	
Days in hospital	1,017 (4.1%)	2,423 (4.9%)	1,925 (4.0%)	−4 (−15 to +6)	0 (−13 to +13)	+4 (−9 to +16)
Duration per admission (median IQR)	7 (4 to 13)	9 (4 to 19)	9 (5 to 16)	−4 (−10 to +2)	0 (−7 to +7)	+4 (−3 to +11)
Patients hospitalised for heart failure	23 (42%)	32 (29%)	38 (36%)		Not analyzed	
Heart failure hospitalizations	36	49	71		Not analyzed	
Other cardiovascular hospitalizations	32	62	52		Not analyzed	
Non-cardiovascular hospitalisations	17	40	36		Not analyzed	
Days in hospital for heart failure	597 (2.4%)	1,163 (2.3%)	912 (1.9%)	−2 (−11 to +7)	−2 (−13 to +9)	0 (−11 to +11)
Duration per heart failure admission (median IQR)	11 (6 to 21)	12 (7 to 21)	9 (6 to 18)	−11 (−24 to +2)	−4 (−18 to +10)	+7 (−8 to +22)
Deaths	28 (51%)	34 (31%)	36 (34%)		Not analyzed	
Circulatory failure	18	26	24		Not analyzed	
Sudden death	7	6	9		Not analyzed	
Other	3	2	3		Not analyzed	
Days lost due to death	8,137 (32.9%)	8,116 (16.4%)	8,841 (18.5%)	+10 (−38 to +57)	−65 (−6 to −123)	−74 (−16 to −132)
Patients dead or with at least one hospitalization	47 (85%)	79 (72%)	81 (76%)		Not analyzed	
Days dead or hospitalized	9,154 (37.0%)	10,539 (21.3%)	10,766 (22.6%)	+6 (−44 to +56)	−65 (−4 to −125)	−71 (−10 to −131)

HTM = home telemonitoring; IQR = interquartile range; NTS = nurse telephone support; UC = usual care.

and telephone contacts, compared with UC. The overall number of contacts also was significantly greater with NTS than HTM during 450 days of follow-up. There was a substantial substitution of home and office visits with telephone contacts with HTM compared with NTS.

DISCUSSION

This study strongly suggests that HTM or a nurse-based heart failure service, using more conventional telephone support (i.e., NTS) can reduce mortality substantially in patients with heart failure and LV systolic dysfunction who have recurrent heart failure admissions. The reduction in mortality is achieved without an increase in the duration of time spent in hospital. Compared with NTS, HTM reduced the duration of hospital admissions and the number of home or office visits substantially. The combined benefits on mortality and consumption of health care resource suggest that HTM may have an important role in the management of heart failure. Although the primary hypothesis was not proved, this study suggests that HTM may be the most cost-effective solution for the delivery of expert care for patients with heart failure.

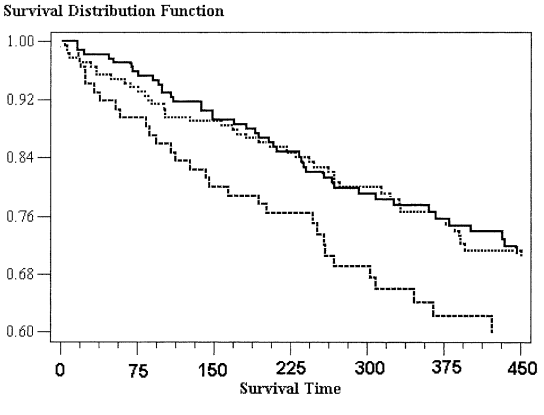

Figure 3. Mortality in each of the randomized groups. A difference was found between usual care and either nurse telephone support or home telemonitoring (chi-squared test: p = 0.0397). The absolute difference in mortality at one year was 16% to 18%. **Dashed line** = usual care; **dotted line** = nurse support; **solid line** = telemonitoring.

Most patients in this trial reported few or no symptoms at the time of assignment despite severe cardiac dysfunction, which may reflect the ability of intensive therapy to control symptoms. Alternatively, the assessment of symptoms in the aftermath of an episode of severe decompensation may be unreliable, either because of the patient's perception that symptoms have improved or because the patient has not yet tried to return to his or her usual activities. Mortality and recurrent hospitalization rates were high, indicating that a simple assessment of symptoms at discharge is not an adequate guide to prognosis. The severity of LV systolic dysfunction, high rates of comorbidity, significant renal dysfunction, and low arterial pressure all predicted a poor prognosis (16). In addition, the median plasma concentration of NT-proBNP was markedly elevated and similar to that reported in studies of severe persistent heart failure (17). This study not only emphasizes that patients with severe cardiac dysfunction and a poor prognosis may have only intermittently severe symptoms but also shows that outcome can be modified if a high standard of care is provided.

Days lost to death or hospitalization, the primary outcome measure in this study, is a relatively novel but highly relevant outcome in clinical and health economic terms.

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Table 6. Results of Multivariate Cox Regression Analysis

Variable	DF	Analysis of Maximum Likelihood Estimates				Hazard Ratio	95% Hazard Ratio Confidence Limits	
		Parameter Estimate	Standard Error	Chi-Square	Pr > Chi-Square			
Random	1	−0.28824	0.14016	4.2290	0.0397	0.750	0.570	0.987
Age	1	0.04734	0.01173	16.2939	<0.0001	1.048	1.025	1.073
BNP, tercile	1	0.50148	0.14546	11.8847	0.0006	1.651	1.242	2.196
BMI	1	−0.08069	0.02871	7.8982	0.0049	0.922	0.872	0.976
Diastolic BP	1	−0.02242	0.00946	5.6145	0.0178	0.978	0.960	0.996
Hemoglobin (g/dl)	1	−0.14745	0.05647	6.8174	0.0090	0.863	0.772	0.964
Sodium	1	−0.04641	0.02335	3.9502	0.0469	0.955	0.912	0.999
Creatinine class	1	0.32216	0.15594	4.2680	0.0388	1.380	1.017	1.873

*Serum creatinine <120 μmol/l, 120 to 200 μmol/l, or > 200 μmol/l.
BMI = body mass index; BNP = brain natriuretic peptide; BP = blood pressure; DF = degrees of freedom.

Kaplan-Meier (time-to-first-event) curves are an accurate method for displaying the effects of treatment on mortality but may be misleading for nonfatal events (18). In "time-to-first-event" analyses for a composite of fatal and nonfatal events, a minor event has the same value as death, and a patient who has a single, short, early admission is ascribed a worse outcome than one who has multiple later, long-term admissions. Hospitalization, especially when brief, may reflect early detection of problems and good care rather than an adverse outcome. Days lost to death or hospitalization, assuming all patients are followed for a similar time, combines mortality with a more sensible measure of morbidity; the number of days spent in hospital.

There are several reasons why increased monitoring by nurses or telemonitoring might improve outcome in this population. Better organization of care and patient support might increase the likelihood of patients being initiated and maintained on appropriate treatment for heart failure. This hypothesis was confirmed for HTM but not for NTS. Earlier detection of cardiovascular and noncardiovascular problems by well-organized care also may have led to more prompt and effective therapy for a variety of problems, both cardiovascular and noncardiovascular.

Two recent reports support the notion that telemonitoring may improve mortality in patients with heart failure. The Weight Monitoring in Heart Failure (WHARF) trial reported a 10.4% absolute and 56.2% relative reduction in mortality during an average follow-up of 169 days in 280 patients with a HTM system for symptoms and weight compared with UC (14). In one of the largest trials of disease management for heart failure, a 5% absolute and 38% relative reduction in mortality was reported with NTS compared with UC among patients with heart failure due to LV systolic dysfunction but not those without systolic dysfunction (12). The fact that benefit occurred only in the group of patients in whom pharmacologic interventions have been shown to reduced mortality provides supportive evidence that this response was rather specific to the management program and not just a general response to improved care. However, neither study showed a reduction in hospitalizations or other healthcare use. Perhaps it is time to move away from always imputing an adverse outcome to healthcare contacts or hospitalizations in trials and service audits. If such events improve how patients feel and reduce their mortality then, provided they are affordable, they should be welcomed, especially when they prevent rather than respond to crises.

Patients assigned randomly to NTS spent the highest proportion of days in hospital, which appears to reflect, on the one hand, the high mortality rate in the UC group, because death prevents hospitalization and, on the other hand, a reduction in hospital days with HTM. The reasons for the reduction in days spent in hospital by HTM appear complex. Patients were more likely to be hospitalized with heart failure in this group, perhaps reflecting the early

Table 7. Summary of Forward Selection

Step	Variable Entered	Number In	Score Chi-Square	Pr > Chi-Square
1	BNP, tercile	2	32.6540	<0.0001
2	Age	3	21.2488	<0.0001
3	Sodium	4	9.2459	0.0024
4	Hemoglobin (g/dl)	5	7.1722	0.0074
5	BMI	6	6.5690	0.0104
6	Diastolic BP	7	5.7513	0.0165
7	Creatinine class	8	4.2956	0.0382

BMI = body mass index; BNP = brain natriuretic peptide, BP = blood pressure.

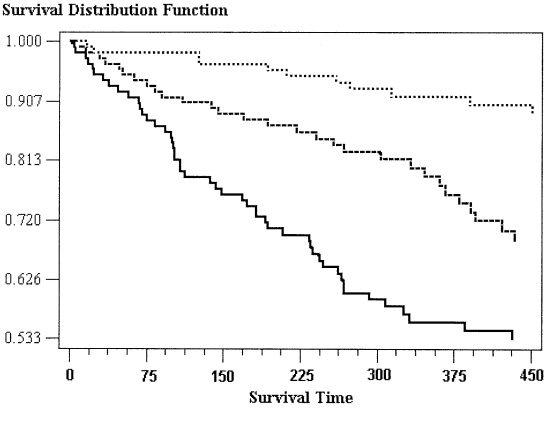

Figure 4. Overall mortality for patients with patients in the lowest (tercile 1: <1,742 pg/ml), mid- (tercile 2: 1,743 to 5,210 pg/ml), and highest (tercile 3: >5,211 pg/ml) tercile of N-terminal pro-brain natriuretic peptide; p = 0.0006 (chi-squared test) for the difference. **Dotted line** = tercile 1; **dashed line** = tercile 2; **solid line** = tercile 3.

Table 8. Patient Contacts Not Resulting in Hospitalization

	240 Days			450 Days		
	UC*	NTS	HTM	UC#	NTS	HTM
Number of patients	85	170	163	55	110	106
Total days at risk†	16,089	33,803	33,641	15,596	38,961	36,934
Emergency room visits						
Visits	8	54	60	13	60	67
Total/1,000 days at risk (95% CI)	0.5 (0.2 to 0.8)	1.6 (1.2 to 2.0)	1.8 (1.3 to 2.2)	0.8 (0.4 to 1.3)	1.5 (1.2 to 1.9)	1.8 (1.4 to 2.3)
Office visits						
Family practitioner	119	602	454	103	591	504
Specialist	34	117	100	46	139	133
Nurse and other	36	104	100	36	113	118
Total	189	823	654	185	843	755
Total/1,000 days at risk (95% CI)	11.7 (10.1 to 13.4)	24.3 (22.7 to 26.0)	19.4 (18.0 to 20.9)	11.9 (10.2 to 13.6)	21.6 (20.2 to 23.1)	20.4 (19.0 to 21.9)
Home visits						
Family practitioner	42	185	162	25	192	140
Specialist	0	3	1	0	3	3
Nurse and other	27	206	128	19	488	94
Total	69	394	291	44	683	237
Total/1,000 days at risk (95% CI)	4.3 (3.3 to 5.9)	11.7 (10.5 to 12.8)	8.7 (7.7 to 9.6)	2.8 (2.0 to 3.7)	17.5 (16.2 to 18.8)	6.4 (5.6 to 7.2)
All face-to-face patient contacts						
Total	300	1,388	1,115	242	1,586	1,059
Total/1,000 days at risk (95% CI)	18.6 (16.6 to 20.7)	41.1 (38.9 to 43.2)	33.1 (31.2 to 35.1)	15.5 (13.6 to 17.5)	40.7 (38.7 to 42.7)	28.7 (29.7 to 33.2)
Telephone calls						
Total	90	914	1,180	102	1,020	1,161
Total/1,000 days at risk (95% CI)	5.6 (4.4 to 6.8)	27.0 (25.3 to 28.8)	35.1 (33.1 to 37.0)	6.5 (5.2 to 7.8)	26.2 (24.6 to 27.8)	31.4 (29.7 to 33.2)
All patient contacts						
Total contacts	390	2,302	2,295	344	2,606	2,220
Total/1,000 days at risk (95% CI)	24.2 (21.9 to 26.6)	68.1 (65.4 to 70.8)	68.2 (65.5 to 70.9)	22.1 (19.8 to 29.4)	66.9 (64.4 to 69.9)	60.1 (57.7 to 62.5)

*Note that patient contacts were evaluated only once every four months in the usual care group compared with monthly in the other two groups, which may have led to under-reporting of contacts. †Days at risk means days-alive and out of hospital.

CI = confidence interval; HTM = home telemonitoring; NTS = nurse telephone support; UC = usual care.

detection of deterioration and possibly some false alarms. However, hospital stays were shorter for patients assigned to HTM, which may reflect improved planning of both admissions and discharges so that effective care was delivered quickly by appropriately trained staff. In addition, there may have been a greater willingness to discharge a patient knowing that monitoring and titration of therapy could be facilitated at home. In this context, it could be argued that many of these hospitalizations were appropriate, contributed to the continued well-being of the patient, and that HTM was encouraging a more flexible and dynamic use of a greater spectrum of resources appropriate to patients' needs.

Improved access to care, either by nurses or by telemonitoring, appeared to lead to an increase in patient contacts, which is not surprising. Home visits are potentially an expensive method of delivering health care because the health care professional may spend considerable time traveling to and from the patients home, although visiting the patient in his or her home environment may help ensure that the patient is complying with medication and coping with his or her situation (8). Office visits make fewer demands on the healthcare professional's time but more demands on the patient, including time and travel costs. By comparison, telephone calls are an inexpensive way of making healthcare contacts. In the context of the TEN-HMS study, substituting a large proportion of face-to-face contacts with telephone calls does not appear to have an adverse effect on the uptake of therapy, symptoms, hospitalization, survival, or patient satisfaction when supported by telemonitoring.

Although many patients were elderly, their acceptance and ability to cope with the HTM technology was high. Few patients asked for the equipment to be removed or failed to comply with daily measurements. Good or very good satisfaction with HTM was reported by 96% of patients.

This trial is one of the first substantial, prospective, randomized ones for HTM for patients with heart failure. The results are sufficiently encouraging to warrant both

service development and further research. Improved selection of patients and tailoring the duration of HTM to the patient's needs could enhance the benefits and lower the costs of therapy further. There was little practical experience of HTM for heart failure when this study was planned, and nurses and medical staff had to learn how to use the technology as the study progressed. Staff training programs based on this study also could improve the effectiveness of HTM. Finally, improvements in devices, communication, and data processing for decision support all are likely to increase the potential of HTM to benefit patients.

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Reprint requests and correspondence: Prof. John G. F. Cleland, Department of Cardiology, University of Hull, Castle Hill Hospital, Kingston-upon-Hull, United Kingdom. E-mail: j.g.cleland@hull.ac.uk.

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APPENDIX

For a list of the Steering Group and Investigators, please see the May 17, 2005, issue of *JACC* at www.onlinejacc.org.