Congestive Heart Failure

Randomized trial of a daily electronic home monitoring system in patients with advanced heart failure: The Weight Monitoring in Heart Failure (WHARF) trial

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Background Heart failure treatment guidelines emphasize daily weight monitoring for patients with heart failure, but data to support this practice are lacking. Using a technology-based heart failure monitoring system, we determined whether daily reporting of weight and symptoms in patients with advanced heart failure would reduce rehospitalization and mortality rates despite aggressive guideline-driven heart failure care.

Methods This was a randomized, controlled trial. Patients hospitalized with New York Heart Association class III or IV heart failure, with a left ventricular ejection fraction $\leq35\%$ were randomized to receive heart failure program care or heart failure program care plus the AlereNet system (Alere Medical, Reno, Nev) and followed-up for 6 months. The primary end point was 6-month hospital readmission rate. Secondary end points included mortality, heart failure hospitalization readmission rate, emergency room visitation rate, and quality of life.

Results Two hundred eighty patients from 16 heart failure centers across the United States were randomized: 138 received the AlereNet system and 142 received standard care. Mean age was 59 ± 15 years and 68% were male. The population had very advanced heart failure, New York Heart Association class III (75%) or IV (25%), as evidenced by serum norepinepherine levels, 6-minute walk distance and outcomes. No differences in hospitalization rates were observed. There was a 56.2% reduction in mortality ($P < .003$) for patients randomized to the AlereNet group.

Conclusions This is the largest multicenter, randomized trial of a technology-based daily weight and symptom-monitoring system for patients with advanced heart failure. Despite no difference in the primary end point of rehospitalization rates, mortality was significantly reduced for patients randomized to the AlereNet system without an increase in utilization, despite specialized and aggressive heart failure care in both groups. (Am Heart J 2003;146:705–12.)

The recent American College of Cardiology/American Heart Association Guidelines for the Management of Heart Failure recommend daily weight monitoring as a cornerstone for the management of patients with heart failure.[1] This recommendation has been widely accepted despite the lack of prospective, randomized data evaluating the efficacy of this strategy on objective clinical outcomes. Heart failure guidelines have

prompted the development of disease management programs driven by patient self-assessment and self-reporting of changes in weight and symptoms. Comprehensive heart failure disease management programs rely heavily on primary management by nurses as patients self-report changes in weights and symptoms.[2,3] These contacts with patients are usually not performed on a daily basis. A recent review of randomized trials of disease management programs in heart failure found that only programs that required specialized follow-up by a multidisciplinary team reduced hospitalizations, although data on mortality was inconclusive.[4]

In contrast to these personnel and cost intensive disease management programs, several small, uncontrolled, nonrandomized, single center studies have suggested that the use of a technology-based strategy to provide daily monitoring of patients with heart failure may be effective in reducing hospitalization rates, without any observed improvement in mortality.[5,6] Accordingly, we conducted a prospective, randomized, multicenter trial to determine whether a technology-based, physician-directed daily weight and symptom monitoring system would reduce rehospitalization rates, and we also assessed the impact of the technology on mortality and health-related quality of life in patients admitted to the hospital with decompensated, advanced heart failure secondary to systolic dysfunction.

Methods

Study population

Patients hospitalized with New York Heart Association (NYHA) class III or IV heart failure, with a left ventricular ejection fraction, measured within 6 months of enrollment, of ≤35% were eligible for enrollment. These patients had to weigh <400 pounds (scale limit), have the ability to stand for at least 20 seconds without holding the wall, and speak either English or Spanish.

Patients were recruited from 16 clinical sites throughout the continental United States (8 cardiac transplant centers and 8 community-based cardiology practices). Patients were followed-up by cardiologists experienced in the management of heart failure throughout the study. Most of the centers had dedicated heart failure programs.

Treatment with a diuretic and vasodilator was required. Digoxin and β-blocker use were allowed. Patients were excluded if they had unstable coronary syndromes (unstable angina, angina-limited exercise, or myocardial infarction within the 8 weeks before enrollment), primary valvular heart disease (primary stenotic valvular heart disease, a malfunctioning prosthetic heart valve), primary myocardial disease (obstructive cardiomyopathy, amyloidosis, or active myocarditis), pericardial disease, uncorrected thyroid disease, advanced renal disease (dialysis or creatinine >4.0 mg/dL), or requirement for chronic inotropic therapy. Patients with a heart transplant, an anticipated survival <6 months, or no phone line in their home were also excluded.

Institutional review board approval was obtained in all participating institutions, and all patients provided written informed consent.

Procedures

After informed consent was obtained and screening laboratory evaluations were completed, patients were randomized to receive continued standard outpatient heart failure therapy plus the AlereNet system (Alere Medical, Reno, Nev) or standard outpatient heart failure therapy including a recommendation to use a standard scale for daily weight assessment. For most patients, standard heart failure care included participation in a dedicated heart failure program with additional nursing resources. Before discharge, all patients were educated about heart failure, including advice on daily weights, dietary restrictions including sodium and fluid, and signs and symptoms of a heart failure decompensation. Patients were advised to report these changes in weight and symptoms to their physician.

Patients randomized to the standard care control group were instructed to contact their physician for weight increases of more than a prespecified amount or if their symptoms of heart failure worsened. These patients were asked to bring a copy of their home weight log to study visits. Follow-up visits, other than study visits, were at the discretion of the treating physician. Telephone contacts were permitted at the discretion of the treating physician or nurse.

Patients randomized to the intervention received the AlereNe monitoring system using the DayLink monitor. The system includes an electronic scale placed in patients' homes and an individualized symptom response system (DayLink monitor) linked via a standard phone line using a toll-free telephone number to a computerized database monitored by trained cardiac nurses employed by Alere, Incorporated (Figure 1). Patients were instructed to weigh themselves and respond to yes/no questions about heart failure related symptoms twice daily. The attending physician individualized the symptom questions and weight goals for each patient at the time of enrollment. The AlereNet nurses reviewed the patient's weights and responses on a daily basis (7 days/week, 365 days/year) and contacted the patient as necessary to verify any changes observed in symptoms or weight, per an individualized intervention protocol. Increases in weight beyond a prespecified amount and/or changes in the patient's symptoms were promptly reported to the physician by these nurses. These reports were made by a summary fax and direct verbal contact of the changes in symptoms and weights.

Baseline data collection included patient demographics, medical history, prior heart failure hospitalizations, etiology of heart failure, duration of heart failure, physical examination, left ventricular ejection fraction, laboratory results, electrocardiographic data, 6-minute walk test, medications, serum norepinepherine level, quality of life and satisfaction measurements. Supine baseline serum norepinepherine specimens were collected 30 minutes after the insertion of an intravenous catheter while subjects were resting in a darkened room. A central core laboratory (Specialty Laboratories, Santa Monica, Calif) was used for analysis of norepinepherine levels. Norepinepherine levels were obtained within 2 weeks of discharge from the index hospitalization.

Clinical data for the trial were collected via in-person assessments by trained clinicians at discharge from the baseline hospitalization, and at 2 weeks, 3 months and 6 months. Laboratory tests, including electrolytes and renal function, medications, and physical exams were obtained at each of these visits. Repeat 6-minute walk test, quality of life and satisfaction measurements also were obtained at the 6-month visit. Patients were followed-up for 30 days after their 6-month visit to obtain additional hospitalization data after disenrollment. For all patients, including drop outs, vital status was obtained at the 6-month and 6-month-plus-30-days time points.

To insure that all hospitalizations, emergency room visits, and deaths were identified, all patients were contacted by telephone on a monthly basis by a nonmedical surveyor (blinded to patient treatment group randomization), located outside of the enrollment sites and Alere monitoring center. Records were obtained for each of these events, including those occurring outside of the participating health systems.

End points

The primary end point for the study was 180-day hospital readmission rate. Secondary end points included mortality rate, heart failure hospitalization readmission rate, emergency room visitation rate, quality of life measurements including the Medical Outcome Study 12 Item Short Form (SF-12),[7] Medical Outcomes Study Health Distress Scale,[8] Minnesota Living with Heart Failure Questionnaire,[9] and overall Patient Satisfaction (single item) with heart failure care.

Statistical analysis

All analyses were performed on an intent-to-treat basis. Baseline comparability of intervention and usual care groups was assessed using t tests and χ^2 tests. Major end points including time to first rehospitalization (all causes), heart-failure rehospitalization, death, and the combined end point of death or first rehospitalization were examined using Kaplan-Meier survival curves and log rank tests. Categorical outcomes such as the proportion of patients who died at home or who sought care through emergency departments were examined using appropriate χ^2 tests. Statistical significance was determined if the null hypothesis could be rejected at the $P < .05$ level.

Results

From July 1998 through December 2000, a total of 280 patients from 16 medical centers across the United States underwent randomization: 138 received the AlereNet system plus standard heart failure care and 142 were assigned to receive standard heart failure care. The mean age of the population was 59 ± 15 years and 68% were male. The mean follow-up period was 169 ± 51 days. During the study, 32 patients either refused follow-up data collection or were lost to follow-up. Seven patients received cardiac transplantation and were censored on the day of transplant. Excluding deaths, there was no difference between groups in the percentage of patients who failed to complete 6 months of follow-up. Vital status on every
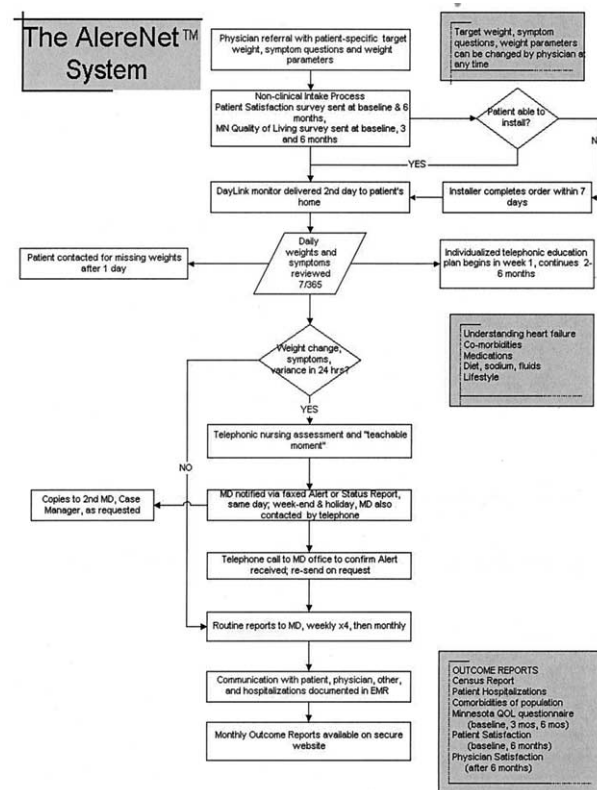
The AlereNet System.

patient with the exception of two was established at the end of the study period. Both patients with unknown vital status were in the standard care group.

As shown in Table I, the 2 groups had comparable characteristics at baseline, including medications, 6-minute walk distance, ejection fraction, serum creatinine, sodium and norepinepherine levels (consistent with NYHA class III/IV symptoms). No difference in the baseline Minnesota Living with Heart Failure Questionnaire, SF-12 and Health Stress questionnaires was observed between the groups.

Compliance with the monitoring system in the AlereNet arm was 98.5%. Non compliance was defined as patient measurements not received for ≥ 2 calendar days (missing 2 morning weights) for reasons other than hospitalization, vacation, physical condition that precludes weighing, or secondary to technical difficulties. A total of 1181 alerts were sent to the physicians managing the 138 patients in the AlereNet arm over the course of the study.

Readmission rates

No difference was observed between the intervention and standard care groups in the overall time to

Table I. Demographic and clinical characteristics of intervention and standard care group patients at baseline (n = 280)

	No.	Standard care	AlereNet	P
Overall		142	138	
Sex	280			.47
Male		93 (65.5)	96 (69.6)	
Female		49 (34.5)	42 (30.4)	
Race	280			.58
White		87 (61.3)	92 (66.7)	
African American		46 (32.4)	40 (29.0)	
Other		9 (6.3)	6 (4.4)	
Married	280	77 (54.2)	77 (55.8)	.79
Living alone	280	30 (21.1)	26 (18.8)	.63
Age (y)	280	60.2 ± 14.9	57.9 ± 15.7	.23
Medical history				
CVA/TIA	280	19 (13.4)	21 (15.2)	.66
Bypass surgery	279	39 (27.7)	30 (21.7)	.25
Diabetes mellitus	280	58 (40.9)	57 (41.3)	.94
Smoking	279	88 (62.4)	86 (62.3)	.99
Afib/flutter	280	48 (33.8)	50 (36.2)	.67
Hyperlipidemia	280	56 (39.4)	49 (35.5)	.50
Hypertension	280	93 (65.5)	84 (60.9)	.42
Myocardial infarction	280	56 (39.4)	53 (38.4)	.86
Pacemaker	280	24 (16.9)	25 (18.1)	.79
Implantable cardiovertor/defibrillator	280	23 (16.2)	25 (18.1)	.67
Duration of CHF (months)	279	45.4 ± 59.7	42.3 ± 48.0	.64
Cardiomyopathy cause	279			.38
Ischemic		65 (46.1)	55 (39.9)	
Idiopathic		58 (41.1)	58 (42.0)	
Other		18 (12.8)	25 (18.1)	
NYHA class	273			.86
III		106 (75.2)	100 (75.8)	
IV		35 (24.8)	32 (24.2)	
Lab results				
Creatinine	280	1.46 ± 0.62	1.44 ± 0.61	.71
Sodium	280	137.1 ± 4.0	136.4 ± 4.2	.17
Norepinepherine	222	714.9 ± 434.5	735.9 ± 439.2	.75
LVEF %	280	21.8 ± 6.8	21.6 ± 6.8	.72
6-Minute walk (feet)	272	690.0 ± 413.2	700.4 ± 373.3	.83
Medication				
Diuretic	280	135 (95.1)	134 (97.1)	.38
ACE Inhibitor	280	104 (73.2)	102 (73.9)	.90
Digoxin	280	112 (78.9)	123 (89.1)	.02
β-Blocker	280	52 (36.6)	53 (38.4)	.76
Amiodarone	280	33 (23.2)	31 (22.5)	.88
Warfarin	280	54 (38.0)	61 (44.2)	.29
ASA	280	67 (47.2)	65 (47.1)	.99
Angiotensin receptor Blocker	280	21 (14.8)	24 (17.4)	.55
SF-12 QOL scores				
Baseline Physical CS	265	32.1 ± 8.7	31.7 ± 7.3	.64
Baseline Mental CS	265	40.8 ± 10.8	42.2 ± 10.8	.29
Minnesota Living with Heart Failure	277	65.3 ± 22.6	67.9 ± 23.9	.37
Health Distress	277	19.7 ± 8.2	20.3 ± 8.3	.53

Values are presented as number (%) or mean ± SD.

death or first rehospitalization (Figure 2). There was also no difference in time to first emergency department visit, total number of emergency department visits, total number of hospitalizations, or total num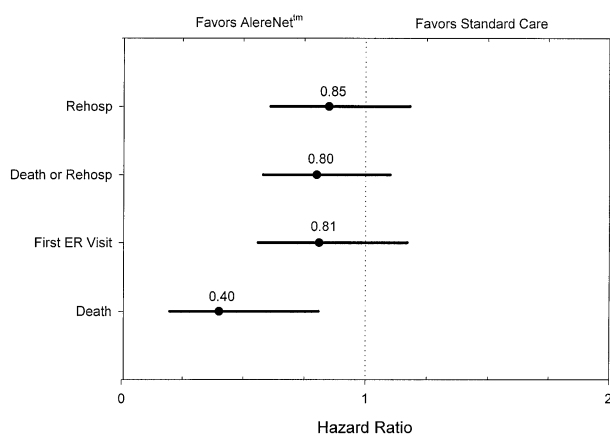ber of cardiovascular hospitalizations between the groups (Figure 3, Table II). This remained true even when events were standardized by time at risk. Inpatient length of stay, cardiac intensive care unit days, and step down unit days were also not different between the groups.

Figure 2
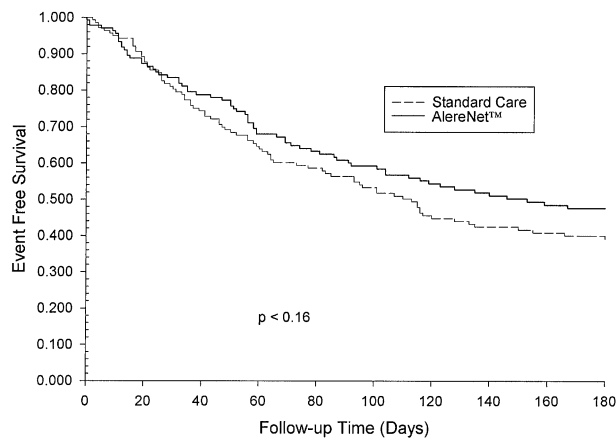
Kaplan-Meier curves of time to death or first rehospitalization for AlereNet versus standard heart failure care.

Figure 3

Hazard ratios with 95% CIs of outcomes.

Table II. Utilization and quality of life measures

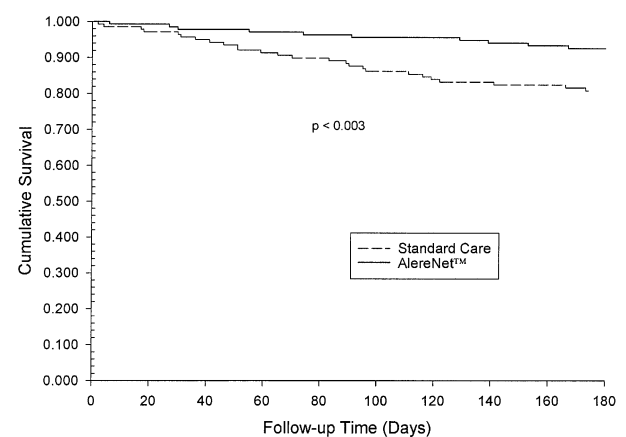|	Standard care	AlereNet	P*
Average utilization ± SD†			
All rehospitalizations	0.20 ± 0.30	0.19 ± 0.46	.28
Cardiovascular rehospitalizations	0.11 ± 0.26	0.08 ± 0.24	.28
Average change in quality of life ± SD‡			
Minnesota Living with Heart Failure score	−23.3 ± 26.9	−27.8 ± 23.8	.22
SF-12 Physical Summary score	4.3 ± 11.4	6.7 ± 10.4	.15
SF-12 Mental Summary score	5.2 ± 13.2	5.9 ± 10.6	.73
Health Distress score	5.5 ± 8.8	4.8 ± 8.3	.57

All quality of life change scores indicated improvement between baseline and follow-up.
*P values are based on Wilcoxon rank sum tests for average utilization, and on *t* tests for average changes in quality of life.
†Utilization estimates represent the average utilization per patient per month of follow-up, over the first 6 months of the trial.
‡Quality of life estimates represent the average change over 6 months.

Figure 4

Kaplan-Meier survival curves for AlereNet System versus standard heart failure care.

Mortality

Over the course of the 6-month follow-up, there were 26 (18.4%) deaths in the standard care group and 11 (8.0%) deaths in the AlereNet group, representing a 56.2% difference in mortality (Figure 3, Figure 4) ($P < .003$). The number of patients needed to treat in order to save one life was 9.7 patients. The survival curves began to separate by approximately 30 days after enrollment. As shown in Table III, there were no differences between the groups in the etiology or location of death. The impact on mortality was observed at both cardiac transplant as well as nontransplant centers. Although we did not have statistical power for

site-specific analyses, we saw no evidence that the mortality benefit was limited to patients enrolled from 1 or 2 sites. In the 30 days after disenrollment from the study, the mortality benefit persisted.

Quality of life measures

Among patients completing their 6-month follow-up visit, patients in both groups experienced improvement between baseline and 6 months in their Minnesota Living with Heart Failure, SF-12 and Health Distress scores (Table II). Although no difference was

Table III. Characteristics of intervention and standard care patients who died during the study

	Standard care	AlereNet	P
Deaths	26	11	
Cause of death (%)*			.96
Sudden cardiac death	6 (24.0)	3 (27.3)	
Progressive heart failure	8 (32)	4 (36.4)	
Fatal myocardial infarction	3 (12.0)	0 (0.0)	
Arrhythmia	2 (8.0)	1 (9.1)	
Other vascular	2 (8.0)	1 (9.1)	
Noncardiovascular	2 (8.0)	1 (9.1)	
Cannot be determined	2 (8.0)	1 (9.1)	
Place of death (%)			.61
Home	9 (36.0)	3 (27.3)	
Hospital	16 (64.0)	8 (72.7)	
Sex (%)			.31
Male	17 (65.4)	9 (81.8)	
Female	9 (34.6)	2 (18.2)	
Age (y) (mean ± SD)	67.2 ± 14.3	64.8 ± 9.1	.6
Days to death (mean ± SD)	73.9 ± 47.6	101 ± 71.5	.2

*One usual care patient is missing cause of death and place of death information because the patient was reported dead after failing to complete follow-up visits.

statistically significant, the intervention group trended towards improvement in all quality of life measures. Due to differential drop outs between the groups, all scores at 6 months were compared for all patients (including deaths and drop outs) by carrying their baseline quality of life scores forward. This did not affect the outcome of the analyses.

Discussion

This study is the first multicenter, prospective, randomized, controlled clinical trial to examine the effect of a technology-based heart failure daily weight and symptom management system on hospitalization rates, mortality, and quality of life in patients hospitalized with advanced heart failure (ie, as measured by plasma norepinepherine levels, 6-minute walk distance, ejection fraction, serum sodium and creatinine and outcomes). Although not designed as a mortality study, we demonstrated that use of the AlereNetm monitoring system using the DayLink monitor resulted in a reduction in 6-month mortality rate in these high-risk heart failure patients managed by heart failure specialty cardiologists in the setting of experienced heart failure centers. Despite aggressive medical management in both arms of the study, this nondrug, daily monitoring technology intervention provided an additional mortality benefit beyond guideline recommended care for patients with advanced heart failure.

The expectation was that there would be a reduction in utilization as measured by reductions in hospitalization as observed with this specific technology in a large population managed primarily by internists and primary care physicians.[10] However in this prospective, randomized trial, where patients were selected by specific inclusion and exclusion criteria and, further, managed by experienced cardiologists with heart failure expertise, this reduction in utilization was not observed. Surprisingly, a significant reduction in all-cause mortality was observed. This mortality effect has been suggested in other randomized trials utilizing intensive home-based nursing-driven multidisciplinary interventions.[11]

Across the entire group, the utilization parameters could not explain the impact on mortality. The length of stay, number of hospitalizations and utilization of intensive care unit resources were similar between the groups. Why then did the intervention reduce mortality? Patients in the intervention group received daily electronic monitoring and evaluation of their symptoms by trained nurses. This allowed for possible rapid assessment and intervention for patients early in the course of a heart failure decompensation 7 days per week. Intervention nurses contacted patients' physicians to report any potentially important symptom or weight changes. There was no facilitation of the communication between patients and physicians in the standard care arm, although there was also no restriction on contacts. In the standard care arm, patients were also aggressively treated, as manifested by medication utilization that reflected excellent compliance with published guidelines during the course of the study. At 6 months, excluding deaths and drop outs, 74% of the standard care and 70.5% of the intervention patients were receiving angiotensin-converting enzyme inhibitors and 30.2% and 23.8%, respectively, were on angiotensin-receptor blockers. β-Blocker use increased significantly in both groups, with 70.8% of the standard care patients and 67.6% of the intervention patients receiving β-blockers at the end of the study. This is consistent with the practice at the time to initiate and titrate β-blockers after a patient had been discharged from the hospital and was stable after a heart failure exacerbation. There were no statistically significant differences of medication use between the groups at 6 months. Most of the patients in the study received heart failure care that met or exceeded published guidelines.

One major difference in this study compared with others that have reported reductions in utilization with this technology is that these patients were managed strictly by cardiologists and, further, cardiologists with specialized heart failure expertise.[10] In this context, these cardiologists were likely more able to utilize the data generated from the DayLink monitoring system to optimize the care of these patients either in the home setting or in settings in which hospitalization was truly appropriate. Therefore, we believe that the hospitaliza-

tion frequency for these very ill patients was truly a marker of progression of the heart failure state and therefore would not be expected to differ between treatment groups. Heart failure hospitalizations may not be a failing of the patient's own personal heart failure care regimen (the compliance rate with the technology intervention was extremely high) but rather a manifestation of their progressively advanced disease state. The only effect of this technology intervention was a major mortality reduction, as observed in this trial, which was potentially a more accurate marker of the acuity and progression of the heart failure state in these patients as opposed to a measurement of utilization, such as rehospitalization rates.

It is also important to note that we did not observe an increase in utilization in this study. Previous studies of high-risk patients have shown increases in utilization associated with improved access to care. For example, in a study of veterans hospitalized with chronic diseases including heart failure, an intervention involving intensive follow-up by primary care physicians and nurses increased hospitalization rates and utilization compared to those in the usual care group.[12] The intervention we studied appears to improve survival rates without increasing utilization.

Our study has several limitations. First, these observations are limited to patients with advanced heart failure with an extremely high predicted-mortality rate. Further, although an ideal study would include an even larger sample size, this is the largest multicenter randomized heart failure technology intervention trial to date. The fact that our patients were randomized from 16 heart failure centers across a wide range of geographic and practice settings enhances the generalizability of the findings. We cannot exclude that chance led to the result of decreased mortality, especially as mortality was not the primary end point for this trial.[13] Positive secondary end points in the setting of a negative primary end point have been misleading in other randomized clinical trials of heart failure treatments.[14] Although we prospectively captured all hospitalization events in a rigorous and complete manner, cost data were not collected. Also, we did not collect data at all outpatient visits during the study, but rather only those mandated by the protocol. Finally, follow-up quality of life measurements were obtained only at the 6-month visit. Patients who died or dropped out before completing the study did not complete follow-up quality of life surveys, limiting our ability to understand the full impact of the intervention. As a result, short-term changes in quality of life may have been missed.

This study is the first to demonstrate a mortality benefit in patients with advanced heart failure cared for with an outpatient, technology-based, cardiologist-directed, in-home daily heart failure weight and symptom monitoring system despite very aggressive and optimal guideline driven heart failure care by experienced clinicians. The question of whether application of this technology intervention to other lower-mortality–risk heart failure populations or primary-care-physician-managed populations would reduce utilization remains to be determined.

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Appendix

The centers and investigators participating in the WHARF trial are listed below, with the number of patients randomized at each center given in parentheses. For each center, the first person listed was the principal investigator.

The Care Group, LLC, Indianapolis, IN (44): M.N. Walsh and J.L. Mullennax; University of Pennsylvania Health System, Philadelphia, PA (38): L.R. Goldberg, E. Loh and L.A. Hopton; The Sanger Clinic, Carolinas Medical Center, Charlotte, NC (30): T.A. Frank, K. Hinson, M. Whitney, and R. Keyes; San Diego Cardiac Center, Sharp Memorial Hospital, San Diego, CA (22): B.E. Jaski and S. Harte; Emory University Hospital, Atlanta, GA (20): A.L. Smith, G. Snell, and K.J. Markow; Chestnut Hill Cardiology, Ltd., Chestnut Hill Hospital, Flourtown, PA (20): R. Rodrigues and T. Bond; Columbia Presbyterian Medical Center, New York, NY (20): D.M. Mancini M.E. Cordisco, and L. Donchez; North Shore University Hospital, Manhassett, NY (19): D. Grossman, A. Spatz, K. Hammond and M.E. Berry; Kelly Cardiovascular Group, Lankenau Hospital, Wynnewood, PA (15): J. F. Burke, S. Heaney and C. Dionisio; University of Utah Medical Center, Salt Lake City, UT (15): D.O. Taylor, K. Walker and M.L. Eidson; Christiana Care Health System, Newark, DE (11): M.E. Stillabower and P. Morelli; Dallas VA Medical Center, Dallas, TX (14): E.J. Eichorn and M.K. Roesle; St. Louis University Hospital, St. Louis, MO (7): P.J. Hauptman, M. Jacobs, and M. Rawlings; Baylor College of Medicine and The Methodist Hospital, Houston, TX (7): G.Torre-Amione and J. Day; UCSF- San Francisco General Hospital, San Francisco, CA (3): T. Nanevicz and S. Ennis; University Hospital, University of Cincinnati College of Medicine, Cincinnati, OH (1): W.T. Abraham, L.E. Wagoner and E.A. Hauntz.

Clinical Coordinating Center (Hospital of the University of Pennsylvania): E. Loh, Chairman, L. Goldberg, K. Craig, F. Pickering, V. Hatton; Data Coordinating Center (Center For Health Care Evaluation, VA Palo Alto Health Care System, Stanford University School of Medicine): J. Piette, C. Mah; Core Norepinephrine Laboratory (Specialty Laboratories): M. Weber; Telephone Monitoring: R. Sylvia.