Pharmacist Intervention to Improve Medication Adherence in Heart Failure

A Randomized Trial

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Background: Patients with heart failure who take several prescription medications sometimes have poor adherence to their treatment regimens. Few interventions designed to improve adherence to therapy have been rigorously tested.

Objective: To determine whether a pharmacist intervention improves medication adherence and health outcomes compared with usual care for low-income patients with heart failure.

Design: Randomized, controlled trial conducted from February 2001 to June 2004.

Setting: University-affiliated, inner-city, ambulatory care practice.

Patients: 314 low-income patients 50 years of age or older with heart failure confirmed by their primary care physician.

Intervention: Patients were randomly assigned to intervention (39% [n = 122]) or usual care (61% [n = 192]) groups and were followed for 12 months. A pharmacist provided a 9-month multilevel intervention, with a 3-month poststudy phase. An interdisciplinary team of investigators designed the intervention to support medication management by patients who have low health literacy and limited resources.

Measurements: Primary outcomes were adherence, as measured by using electronic prescription monitors, and exacerbations requiring emergency department care or hospital admission. Secondary outcomes included health-related quality of life, patient satisfaction with pharmacy services, and total direct costs.

Results: During the 9-month intervention period, medication adherence was 67.9% and 78.8% in the usual care and intervention groups, respectively (difference, 10.9 percentage points [95% CI, 5.0 to 16.7 percentage points]). However, these salutary effects dissipated in the 3-month postintervention follow-up period, in which adherence was 66.7% and 70.6%, respectively (difference, 3.9 percentage points [CI, −5.9 to 6.5 percentage points]). Medications were taken on schedule 47.2% of the time in the usual care group and 53.1% of the time in the intervention group (difference, 5.9 percentage points [CI, 0.4 to 11.5 percentage points]), but this effect also dissipated at the end of the intervention (48.9% vs. 48.6%, respectively; difference, 0.3 percentage point [CI, −5.9 to 6.5 percentage points]). Emergency department visits and hospital admissions were 19.4% less (incidence rate ratio, 0.82 [CI, 0.73 to 0.93]) and annual direct health care costs were lower ($–2960 [CI, $–7603 to $1338]) in the intervention group.

Limitations: Because electronic monitors were used to ascertain adherence, patients were not permitted to use medication container adherence aids. The intervention involved 1 pharmacist and a single study site that served a large, indigent, inner-city population of patients. Because the intervention had several components, intervention effects could not be attributed to a single component.

Conclusions: A pharmacist intervention for outpatients with heart failure can improve adherence to cardiovascular medications and decrease health care use and costs, but the benefit probably requires constant intervention because the effect dissipates when the intervention ceases.

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In the United States, 5 million people have heart failure, with total health care costs exceeding $29 billion (1). These costs are largely derived from expensive exacerbations that require emergency visits and hospitalizations (1, 2). Regularly administered cardiovascular medications may preserve cardiac function, improve quality of life, and reduce risk for costly exacerbations. However, patients sometimes do not adhere to prescribed instructions and have poor outcomes (3–5). Researchers have estimated that approximately 50% of patients with chronic illnesses do not take their medications as prescribed (6). Reasons for nonadherence include lack of patient knowledge, skills, and support to appropriately self-manage complicated medication regimens (7, 8).

Although chronic disease management programs abound, few studies have rigorously tested interventions aimed at improving patient adherence to prescribed medications and their effect on health outcomes (9, 10). We conducted a randomized clinical trial to assess the effect of a pharmacist intervention on patients who are socioeconomically disadvantaged and medically vulnerable. We hypothesized that the intervention would improve adherence to heart failure medications, reduce exacerbations requiring emergency department visits or hospitalization, improve disease-specific quality of life, increase patient satisfaction, and reduce health care costs.

See also:

Print
Editors' Notes 715

Web-Only
Appendix Tables
Conversion of figure and tables into slides

Methods

Design Overview

The methods for our randomized trial are described elsewhere (11–13). We recruited patients from the general medicine and cardiology practices of Wishard Health Services, Indianapolis, Indiana, which serves socioeconomically disadvantaged and medically vulnerable patients. The study was conducted from February 2001 to June 2004. Patients took part in the study for 12 months and received 9 months of active intervention by the pharmacist or usual care followed by 3 months of postintervention assessment. Patients in the usual care and intervention groups visited the same pharmacy location, but the intervention pharmacist was instructed to have no contact with patients in the usual care group. The institutional review boards of Indiana University–Purdue University and the University of North Carolina at Chapel Hill approved this study.

Setting and Patients

Indiana University Medical Group, Indianapolis, is an academic primary care group practice composed of primary and specialty care clinics affiliated with Wishard Health Services. Faculty physicians, residents, and nurse practitioners provide care to 13 000 adults (mean age, 57 years [SD, 15]; 60% women; 50% African American). Annually, these patients make approximately 50 000 visits to practices, 72 000 visits to emergency departments, and 135 000 visits to pharmacies and have 16 000 hospitalizations. We recruited patients from 4 identical general medicine practices, 1 cardiology practice, and Wishard Memorial Hospital. Practices met in half-day sessions per week that were attended by 2 or 3 faculty members and 3 to 5 residents or fellows from each practice. Faculty physicians practiced 1 to 5 half-days per week, whereas fellows practiced 1 to 2 half-days per week and residents attended the practice 1 half-day per week.

Outpatients of Wishard Health Services fill their prescriptions at central or decentralized outpatient pharmacies located at the ambulatory care center or at 1 of several satellite pharmacies stationed at neighborhood clinics. Fully stocked decentralized pharmacies serviced all study patients. From February 2001 to January 2003, the study pharmacy was located in a building adjacent to the ambulatory care center. From February 2003 to June 2004, the study pharmacy was moved to a space adjacent to the general medicine practices in the ambulatory care center. Two pharmacists and 1 technician were stationed at the pharmacy. The study pharmacist was instructed to service patients in the intervention group only, and a second pharmacist serviced patients in the usual care group and filled prescriptions to be delivered to patients at outlying clinics. The technician filled prescriptions and read electronic adherence monitors.

Weekly lists of eligible patients were created by using the Regenstrief Medical Record System (Regenstrief Institute, Indianapolis, Indiana) (14, 15). We invited clinically stable patients from general internal medicine practices, a cardiology clinic, and Wishard Memorial Hospital (at discharge) to participate in the study. Of 3034 patients with a diagnosis of heart failure, 1512 met criteria for enrollment. Patients were eligible if they were 50 years of age or older; planned to receive all of their care, including prescribed medications, at Wishard Health Services; had a diagnosis of heart failure confirmed by their primary care physician; regularly used at least 1 cardiovascular medication for heart failure (angiotensin-converting enzyme [ACE] inhibitor or angiotensin-receptor blocker, β-adrenergic antagonist, diuretic, digoxin, or aldosterone antagonist); were not using or were not planning to use a medication container adherence aid (for example, a pill box); had access to a working telephone; and could hear within the range of normal conversation. We excluded patients with dementia. Patients received their prescription medications through state and local assistance plans at no cost. Thus, cost of medicines was not a deterrent to adherence.

Randomization

A trained interviewer conducted a baseline interview at enrollment. Interviewers were blinded to patients' study status and played no role in the delivery of the intervention. Interviewers contacted a centralized data manager at the end of each interview to determine the patient's study assignment, which was otherwise concealed. We randomly assigned patients, without blocking or stratification, to receive the pharmacy intervention or usual care by using a univariate discrete distribution from the IMSL Fortran Library's subroutine RNGDA pseudorandom number gener-

Context

Patients sometimes have difficulty following complicated treatment regimens.

Contribution

In this trial, 314 low-income patients with congestive heart failure were randomly assigned to a pharmacist intervention or usual care. The pharmacist assessed patient knowledge and provided instructions about medication use. During the 9-month intervention, patients in the intervention group had greater medication adherence than patients in the usual care group (79% vs. 68%). These differences dissipated within 3 months of stopping the intervention. Patients in the intervention group also had fewer exacerbations resulting in emergency department visits or hospitalizations than patients in the usual care group.

Implication

Ongoing educational intervention by a pharmacist can improve medication adherence and outcomes in patients with heart failure.

—The Editors

ator (Absoft Corp., Rochester Hills, Michigan) (16). We randomly assigned more patients to the usual care group so that this group could also be a prospective cohort for studying risk factors associated with the clinical deterioration of heart failure. Of the 314 patients included in the study, 229 were recruited from the general internal medicine practices, 15 from the cardiology clinic, and 70 on discharge from the Wishard Memorial Hospital. The numbers of patients assigned to the intervention and usual care groups did not differ by recruitment site ($P = 0.83$).

Intervention

A pharmacist delivered the intervention by using a protocol (**Appendix Table 1**, available at www.annals.org) that included a baseline medication history of all prescription and over-the-counter drugs and dietary supplements taken by patients, which patients brought with them to the baseline interview, and the results of an assessment of patient medication knowledge and skills (7, 8). The pharmacist dispensed enough of the patient's medications to last approximately 2 months.

When medications were dispensed, the pharmacist provided patient-centered verbal instructions and written materials about the medications (11, 13, 17) by using a schema for instruction that has been tested (18, 19). We assigned each medication category an icon (for example, the icon for ACE inhibitors was a red ace of hearts). The same icon appeared on the container label and lid and on the written patient instructions. Written instructions were aimed at patients with low health literacy and contained an easy-to-follow timeline to remind patients when to take their medications (13).

The pharmacist monitored patients' medication use, health care encounters, body weight, and other relevant data by using a study database (20, 21). Information about patients was communicated as needed to clinic nurses and primary care physicians by face-to-face visits, telephone, paging (physician only), and e-mail (physician only). Technicians supported the pharmacist's dispensing efforts within the pharmacy throughout the study. We incorporated costs therein into the economic analysis. Pharmacists serviced patients in the usual care group who were not associated with the intervention or the study.

An interdisciplinary team of investigators that included pharmacists with advanced training in patient education and cardiovascular pharmacotherapy, a geriatrician, a cardiologist with expertise in heart failure, a behavioral scientist, and a cognitive psychologist trained the intervention pharmacist. The intervention pharmacist also studied guidelines for treating heart failure (22), key concepts in the pharmaceutical care of older adults, communication techniques, and the pharmacotherapy of the cardiovascular drugs for heart failure. All pharmacists at Wishard Health Services were aware of the study and were instructed on how to handle and redirect intervention patients who inadvertently arrived at their pharmacy.

Usual Care

Patients in the usual care group were aware of the purpose of the study, and their primary care physicians approved their participation. They received their prescription services from pharmacists who rotated through the study pharmacy. These pharmacists had not received the specialized training provided by the interdisciplinary team to the intervention pharmacist and did not have access to the patient-centered study materials. Aside from an initial medication history taken by the intervention pharmacist before randomization, patients in the usual care group were to have no further contact with the intervention pharmacist. Nonetheless, during the busiest times, patients in the intervention and usual care groups may have been in the pharmacy at the same time.

Outcomes and Measurements

The primary study outcomes were medication adherence tracked by using electronic monitors and clinical exacerbations that required visits to the emergency department or hospitalization. Medication adherence was assessed by electronic monitoring using Medication Event Monitoring System (MEMS) V prescription container lids (AARDEX Ltd., Zug, Switzerland). All prescribed cardiovascular medications were dispensed with MEMS lids that recorded the time and date of each opening and closing onto a digital chip. The same icon was used on the container body and lid to ensure that patients placed the lid on the correct prescription container throughout the study. We used data retrieved from the lids to compute taking adherence and scheduling adherence. Taking adherence is the percentage of prescribed medication taken and measures deviation from the physician's prescription. Scheduling adherence measures the day-to-day deviation in the timing of administration. A medication prescribed for once-daily administration would need to be administered within 2.4 hours of the previous dose (usually taken the preceding day), whereas medications prescribed for twice-daily administration would need to be administered within 1.2 hours of the previous dose (usually taken the preceding day or the same day). Scheduling adherence, as we computed it, measures the reliability or consistency of dosing over time (23, 24).

We measured refill adherence as the medication possession ratio (supplies of medications received relative to amount prescribed) by using prescription records from the Regenstrief Medical Record System (25, 26). We computed results for 1 year, incorporating the 9-month intervention period and the 3-month postintervention period. Because the calculation of refill adherence requires at least 2 refills and patients came for refills at approximately 2-month intervals, we could not compute the refill adherence for the 3-month postintervention period separately. Considering the carry-over effect (to the next refill) of the

intervention that stopped at 9 months, the intervention effect on medication supplies would extend to 11 to 12 months. Hence, we believe that the 12-month period adequately reflects the effect of the intervention. We determined self-reported adherence for the previous month at baseline and 9 months by using validated questionnaires (27, 28). Using these questionnaire scores, we computed a composite score of self-reported adherence (30).

We assessed exacerbations by using hospital admission data from emergency department visits. We extracted data for heart failure–specific, all cardiovascular, and all-cause reasons for emergency visits and hospitalizations; these were adjudicated by a registered nurse abstractor who used a previously validated method (30), from the Regenstrief Medical Record System.

Secondary outcomes included health-related quality of life, satisfaction with pharmacy services, and total direct health care costs. We analyzed disease-specific quality of life by using the Chronic Heart Failure Questionnaire (31), which performs well in the clinical setting of our study (32, 33). This validated questionnaire has 4 dimensions: fatigue, dyspnea, emotion, and mastery. We averaged the scores on each scale, ranging from 1 (worst function) to 7 (best function), across items within each dimension. We assessed satisfaction with pharmacy services by using an internally developed and validated 12-item instrument (Cronbach α level = 0.91). We measured direct health care costs by using fixed and variable intervention costs (26). Fixed costs included training of the intervention pharmacist, material development, programming, and equipment. Variable costs included time spent by the pharmacist delivering the intervention, time spent by physicians speaking with the pharmacist about patients in the intervention group, and costs of written materials. We measured time spent by pharmacists by directly observing them servicing patients at random 3- to 4-hour intervals.

Follow-up Procedures

After study enrollment and baseline interviews, patients returned for interviews at 3, 6, 9, and 12 months. We conducted monthly telephone surveys to collect data on health-related quality of life; ascertain problems associated with electronic monitoring of medication containers and new uses of medication aids, such as pill containers; determine the occurrence of health care use or new prescriptions outside of the study site; and verify address, income, and transportation information. We assessed interviewer blinding by using a computerized closeout protocol at the end of each interview that required interviewers to guess whether each patient was in the intervention or usual care group. The mean ability of the interviewers to correctly guess patients' group assignment was 49% (50% would be predicted if guessing by chance). We determined that the time spent interviewing was similar between intervention and usual care groups for in-person interviews ($P = 0.33$) and telephone interviews ($P = 0.45$).

Patients visited the pharmacy primarily to refill prescriptions. However, patients in the intervention group were encouraged to call or visit the pharmacist for assistance or questions involving their medications. We collected adverse drug event and medication error data by using a program developed for a separate study (34, 35). This program used coded and text data available in the Regenstrief Medical Record System to identify commonly occurring adverse events and medication errors in outpatients. Relevant events included ACE inhibitor–related allergy or cough, toxic serum digoxin concentrations, or use of nonsteroidal anti-inflammatory drugs in persons with high serum potassium concentrations or renal insufficiency. A data safety and monitoring board was kept apprised of all study activities through the receipt of monthly meeting minutes and 3 formal reports.

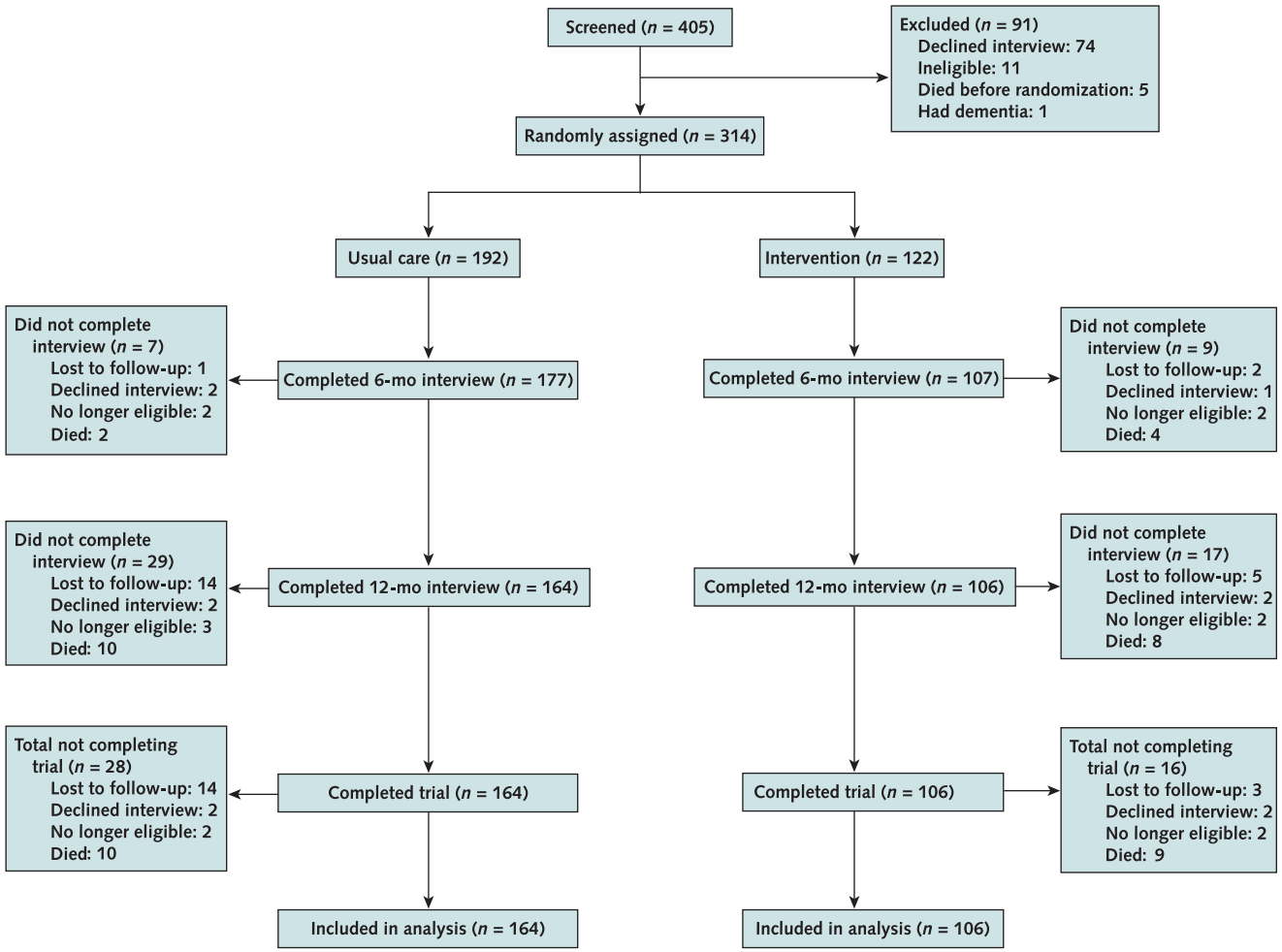
Statistical Analysis

We estimated that a sample size of at least 100 patients in each group would provide 94% power to detect a 10% difference in means for medication adherence by using a *t*-test with a 2-sided α level of 0.05 and assuming a 20% SD. For acute exacerbations, we used a 2-sided log-rank test with proportional events of 0.1 and 0.3 in the intervention and usual care groups, respectively, to estimate that a sample size of 100 patients per group would provide 93% power, when the α level is set at 0.05 and the hazard ratio is constant at 3.38.

We made between-group comparisons by using *t*-tests or the 2-sample Wilcoxon test for continuous variables and chi-square tests for categorical variables. For medication adherence, we compared overall and drug category–specific taking and scheduling adherences. Using data from the MEMS lids, we assessed taking and scheduling adherence, the values of which may range from 0% to 100%. We imputed the data that were missing because of lost medication container lids by using a regression imputation method. We generated 5 imputed MEMS adherence data sets by using SAS PROC MI (SAS Institute, Inc., Cary, North Carolina) from the regression imputation models on the basis of self-reported adherence at baseline and group assignment. We then combined point estimates of the treatment effect from the imputed data sets to achieve valid point and CI estimates by using SAS PROC MIANALYZE (36). Herein, we imputed the overall taking and scheduling adherence outcomes. We did not impute adherence to individual drug classes because patients did not take each medication and we could not justify imputing patients' adherence to medications that were not prescribed. To assess the robustness of the study findings in the presence of missing MEMS adherence measurements, we conducted sensitivity analyses by using 9 scenarios of varying levels of adherence for individuals in the 2 groups who did not complete the trial (**Appendix Table 2**, available at www.annals.org).

Clinical exacerbations were characterized by emer-

Figure. **Study flow diagram.**



gency department visits and hospitalizations. We analyzed the type-specific and overall counts of emergency department visits and hospital admissions by using log-linear regression models that were based on Poisson or negative binomial distributions. To accommodate unequal durations of follow-up, we incorporated the logarithmic duration of follow-up into the log-linear model as an offset parameter. We obtained regression parameters and SEs from the final models. We calculated the incidence rate ratio by exponentiating the parameter estimates. We performed the analysis by using SAS PROC GENMOD, version 9.1. We analyzed changes from baseline for disease-specific quality of life and satisfaction with pharmacy services by using a paired *t*-test. We calculated direct health care costs in 2003 U.S. dollars for the intervention and usual care groups and estimated the between-group difference in costs. To compute the 95% CI around the difference in costs, we used a nonparametric, bias-corrected, accelerated bootstrap approach because of the skewed nature of cost data (37).

To determine whether unintended negative consequences of the intervention were evident, we analyzed the composite of adverse drug events and medication errors. We used the chi-square test to test the hypotheses that the adverse events and errors among patients were independent of group assignment. We also used the method of Krishnamoorthy and Thomson to directly compare rates of these events (38).

Role of the Funding Source

The National Institutes of Health partly funded the study. The funding source had no role in the study design or intervention, recruitment of patients, data collection, analysis, or interpretation of the results, writing of the manuscript, or decision to submit the manuscript for publication.

Results

The **Figure** shows the flow of patients through the study. Compared with all potentially eligible patients (*n* =

1512), the 314 patients enrolled in the study were younger (63 vs. 67 years; $P < 0.001$) and were more likely to be women (67% vs. 59%; $P = 0.009$). At baseline, however, patients were otherwise similar to the total population of patients with heart failure ($n = 3034$; mean age, 60 years), of whom 66% were women. Randomization resulted in well-balanced groups (**Table 1**), except that more patients in the usual care group than the intervention group had a history of coronary artery disease (76% vs. 63%). Follow-up rates were similar in the intervention (87%) and usual care (85%) groups.

The pharmacist dispensed 1004 electronic monitor lids on cardiovascular medication containers. Of the 404 lids dispensed to patients in the intervention group (a mean of 3.3 lids per patient), 330 lids were returned by closeout (81.7%). Of the 600 lids dispensed to patients in the usual care group (a mean of 3.1 lids per patient), 472 lids were returned by closeout (78.7%). The difference in lid returns between groups was not significant ($P = 0.22$). Furthermore, the results of the sensitivity analyses to determine the effect of missing data from lost lids and patient withdrawals indicated that our results were robust to the varying levels of adherence for individuals with missing data (**Appendix Table 2**, available at www.annals.org).

The pharmacist logged 5588 activities. The most common of these were educating patients about their medications, resolving medication problems, reinforcing physicians' instructions to patients about prescribed medications, reminding patients of the importance of adherence and obtaining refills, communicating with physicians, and encouraging important patient lifestyle changes (such as stopping smoking and dietary sodium discretion).

Medication Adherence

Overall taking adherence was 67.9% and 78.8% in the usual care and intervention groups, respectively (difference, 10.9 percentage points [95% CI, 5.0 to 16.7 percentage points]) during the intervention period, but these salutary effects dissipated in the 3-month postintervention follow-up period, in which taking adherence was 66.7% and 70.6%, respectively (difference, 3.9 percentage points [CI, −5.9 to 6.5 percentage points]) (**Table 2**). Taking adherence was statistically significantly greater in the intervention group than the usual care group for the following cardiovascular medications commonly used by patients with heart failure: ACE inhibitors (difference, 10.5 percentage points [CI, 2.8 to 18.2 percentage points]), β-blockers (difference, 14.7 percentage points [CI, 6.4 to 22.9 percentage points]), digoxin (difference, 13.9 percentage points [CI, 3.5 to 24.3 percentage points]), and loop diuretics (difference, 9.8 percentage points [CI, 1.2 to 18.4 percentage points]).

Overall scheduling adherence was 47.2% and 53.1% in the usual care and intervention groups, respectively (difference, 5.9 percentage points [CI, 0.4 to 11.5 percentage points]) during the 9-month intervention (**Table 2**). Similar to that of taking adherence, this effect dissipated during the 3-month postintervention period (difference, 0.3 percentage point [CI, −5.9 to 6.5 percentage points]). Scheduling adherence effects were statistically significantly greater for ACE inhibitors (difference, 7.7 percentage points [CI, 0.3 to 15.2 percentage points]) and β-blockers (difference, 12.1 percentage points [CI, 5.1 to 19.2 percentage points]).

Refill adherence data indicated that patients in both groups were well supplied with medications by the pharmacy. Compared with the usual care group, the intervention group had statistically greater overall refill adherence (2-sample Wilcoxon test) (105.2% vs. 109.4%, respectively; difference, 4.2 percentage points [$P = 0.007$]) and had increased refill adherence for β-blockers (122.2% vs. 108.4%; difference, 13.8 percentage points [$P = 0.002$]), digoxin (86.4% vs. 76.4%; difference, 10.0 percentage points [$P = 0.039$]), and loop diuretics (148.8% vs. 105.0%; difference, 43.8 percentage points [$P = 0.027$]). However, refill adherence of ACE inhibitors was slightly but statistically significantly greater for the usual care group (98.3% vs. 96.9%; difference, −1.4 percentage points [$P = 0.018$]). Finally, differences in self-reported adherence between groups were small. The modest increase in the intervention group (and overall) in the analysis of medians was not statistically significant (1.0 for the intervention group vs. 0.8 for the usual care group; $P = 0.48$, 2-sample Wilcoxon test).

Heart Failure Exacerbations

As shown in **Table 3**, the intervention group had 19.4% fewer exacerbations on the combined end point of hospital admission or emergency department visit (incidence risk ratio, 0.82 [CI, 0.70 to 0.95]). Fewer hospital admissions occurred in the intervention group for the various reasons for admission (heart failure, all cardiovascular, and all-cause). Multivariable models controlling for patient functional class, counts of prescribed drugs, ejection fraction, and comorbid conditions showed that taking adherence was an independent, statistically significant predictor of the number of hospitalizations for heart failure, cardiovascular reasons, and all causes and of all emergency department visits for cardiovascular reasons. Scheduling adherence predicted emergency department visits for heart failure and all causes (data not shown).

Disease-specific quality of life improved from baseline to 6 months and 12 months by 0.28 and 0.39, respectively, for the intervention group compared with 0.21 and 0.24 for the usual care group, respectively ($P = 0.52$ at 6 months; $P = 0.21$ at 12 months). The overall improvement in patient satisfaction from baseline to 12 months was greater in the intervention group than the usual care group (1.0 vs. 0.7; $P = 0.022$).

Total Direct Costs

The overall actual mean fixed cost of developing the intervention and the variable costs of implementing it were

Table 1. **Baseline Characteristics***

Characteristic	Usual Care Group (n = 192)	Intervention Group (n = 122)
Mean age (SD), *y*	62.6 (8.8)	61.4 (7.7)
Sex, *n (%)*		
Women	127 (66.1)	83 (68.0)
Men	65 (33.9)	39 (32.0)
Race, *n (%)*		
Black	100 (52.1)	55 (45.1)
White	90 (46.9)	66 (54.1)
Other	2 (1.0)	1 (0.8)
Sufficient income, *n (%)*†	123 (64)	76 (62)
Mean education (SD), *y*	11 (3)	11 (2)
Married, *n (%)*	50 (26)	34 (28)
Living alone, *n (%)*	72 (38)	45 (38)
Health literate, *n (%)*‡	136 (71)	88 (72)
Insurance type, *n (%)*		
Medicare		
Yes	108 (56.3)	66 (54.1)
No	84 (43.8)	56 (45.9)
Medicaid		
Yes	70 (36.5)	37 (30.3)
No	122 (63.5)	85 (69.7)
NYHA class, *n (%)*		
I	38 (19.8)	23 (18.9)
II	78 (40.6)	51 (41.8)
III	67 (34.9)	43 (35.3)
IV	9 (4.7)	5 (4.1)
Mean ejection fraction (SD)	0.50 (0.16)	0.49 (0.17)
Mean pro-BNP level (SD), *ng/L*	1406 (3486)	1122 (1940)
Mean log-transformed pro-BNP level (SD), *ng/L*	6.0 (1.6)	5.9 (1.6)
Mean body weight (SD), *kg*	92.5 (24.4)	91.5 (25.8)
Mean body mass index (SD), kg/m^2	34.1 (10.2)	34.1 (9.5)
Mean systolic blood pressure (SD), *mm Hg*	135.4 (25.2)	132.9 (23.6)
Mean diastolic blood pressure (SD), *mm Hg*	70.5 (15.6)	68.9 (14.1)
Mean hematocrit (SD), *%*	37.6 (5.7)	37.7 (5.2)
Mean serum creatinine level (SD)		
μmol/L	106.1 (61.9)	106.1 (44.2)
mg/dL	1.2 (0.7)	1.2 (0.5)
Hypertension, *n (%)*	186 (96.9)	114 (93.4)
Coronary artery disease, *n (%)*	146 (76.0)	77 (63.1)
Diabetes, *n (%)*	131 (68.2)	74 (60.7)
Stroke, *n (%)*	29 (15.1)	16 (13.1)
COPD, *n (%)*	67 (34.9)	39 (32.0)
Atrial fibrillation, *n (%)*	27 (14.0)	14 (11.5)
Mean emergency department visits at 1 year (SD), *n*	3.4 (6.0)	3.0 (4.9)
Mean hospital admissions at 1 year (SD), *n*	1.3 (2.4)	1.1 (2.1)
Long-term medications, *n*	11 (4)	10 (4)
Medication type, *n (%)*		
ACE inhibitor		
Yes	137 (71.4)	75 (61.5)
No	55 (28.6)	47 (38.5)
ARB		
Yes	22 (11.5)	16 (13.1)
No	170 (88.5)	106 (86.9)
β-Blocker		
Yes	120 (62.5)	71 (58.2)
No	72 (37.5)	51 (41.8)
Digoxin		
Yes	52 (27.1)	34 (27.9)
No	140 (72.9)	88 (72.1)
Loop diuretic		
Yes	118 (61.5)	69 (56.6)
No	74 (38.5)	53 (43.4)
Thiazide diuretic		
Yes	29 (15.1)	22 (18.0)
No	163 (84.9)	100 (82.0)
Spironolactone		
Yes	31 (16.2)	14 (11.5)
No	161 (83.8)	108 (88.5)

* ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; NYHA = New York Heart Association.
† Income satisfaction was assessed by asking whether the patient has an income that is comfortable, just enough to get by, or not even enough to get by.
‡ Health literacy was measured by using the Short Test of Functional Health Literacy in Adults (54).

Table 2. **Adherence to Cardiovascular Medications***

Adherence	Intervention Period		Postintervention Period	
	Patients, *n*	Doses Taken (95% CI), %	Patients, *n*	Doses Taken (95% CI), %
Taking adherence				
Overall†				
Intervention	122	78.8 (74.9 to 82.7)	122	70.6 (64.9 to 76.2)
Usual care	192	67.9 (63.8 to 72.1)	192	66.7 (62.3 to 70.9)
Difference‡		10.9 (5.0 to 16.7)		3.9 (−2.8 to 10.7)
ACE inhibitor				
Intervention	77	82.9 (78.1 to 87.7)	65	74.7 (67.1 to 82.3)
Usual care	127	72.4 (67.2 to 77.7)	104	72.1 (65.9 to 78.2)
Difference‡		10.5 (2.8 to 18.2)		2.6 (−7.2 to 12.4)
ARB				
Intervention	15	77.1 (59.2 to 95.0)	15	80.0 (63.6 to 96.3)
Usual care	24	71.0 (58.7 to 83.3)	21	55.1 (37.2 to 72.9)
Difference‡		6.1 (−14.2 to 26.4)		24.9 (0.5 to 49.3)
β-Blocker				
Intervention	70	78.7 (73.1 to 84.4)	64	65.2 (56.8 to 73.6)
Usual care	122	64.1 (58.7 to 64.1)	104	63.4 (57.2 to 69.5)
Difference‡		14.7 (6.4 to 22.9)		1.8 (−8.3 to 11.9)
Digoxin				
Intervention	35	89.1 (83.3 to 94.9)	31	84.2 (76.1 to 92.3)
Usual care	50	75.2 (67.4 to 83.0)	43	72.9 (64.1 to 81.8)
Difference‡		13.9 (3.5 to 24.3)		11.3 (−1.0 to 23.6)
Loop diuretic				
Intervention	70	71.5 (65.6 to 77.3)	61	61.5 (53.3 to 69.7)
Usual care	116	61.7 (56.0 to 67.4)	94	60.4 (53.6 to 67.2)
Difference‡		9.8 (1.2 to 18.4)		1.1 (−9.5 to 11.7)
Spironolactone				
Intervention	16	84.4 (72.3 to 96.4)	13	78.3 (61.6 to 95.0)
Usual care	28	69.7 (58.1 to 81.3)	22	73.4 (61.0 to 85.8)
Difference‡		14.6 (−2.8 to 14.6)		4.9 (−14.9 to 24.7)
Scheduling adherence				
Overall†				
Intervention	122	53.1 (49.1 to 57.1)	122	48.9 (43.7 to 54.1)
Usual care	192	47.2 (43.4 to 50.9)	192	48.6 (44.7 to 52.6)
Difference‡		5.9 (0.4 to 11.5)		0.3 (−5.9 to 6.5)
ACE inhibitor				
Intervention	77	60.7 (55.5 to 65.9)	65	54.9 (48.0 to 61.8)
Usual care	127	53.0 (48.1 to 57.8)	104	54.1 (48.3 to 60.0)
Difference‡		7.7 (0.3 to 15.2)		0.8 (−8.4 to 9.9)
ARB				
Intervention	15	55.9 (38.8 to 73.0)	15	63.1 (45.6 to 80.5)
Usual care	24	51.0 (40.1 to 61.8)	21	39.2 (26.4 to 51.9)
Difference‡		4.9 (−13.6 to 23.5)		23.9 (3.7 to 44.2)
β-Blocker				
Intervention	70	49.2 (43.5 to 55.0)	64	39.9 (33.3 to 46.5)
Usual care	122	37.1 (32.9 to 41.3)	104	40.8 (35.7 to 40.8)
Difference‡		12.1 (5.1 to 19.2)		−0.1 (−9.2 to 7.4)
Digoxin				
Intervention	35	66.8 (59.4 to 74.1)	31	61.0 (52.5 to 69.6)
Usual care	50	57.7 (50.2 to 65.2)	43	55.5 (46.7 to 64.2)
Difference‡		9.1 (−1.7 to 19.8)		5.6 (−6.8 to 18.0)
Loop diuretic				
Intervention	70	41.7 (35.8 to 47.5)	61	38.1 (31.6 to 44.5)
Usual care	116	38.3 (33.2 to 43.4)	94	37.9 (32.3 to 43.6)
Difference‡		3.4 (−4.5 to 11.3)		0.2 (−8.5 to 8.8)
Spironolactone				
Intervention	16	57.8 (44.0 to 71.7)	13	54.2 (39.4 to 69.0)
Usual care	28	51.0 (41.3 to 60.7)	22	56.3 (43.7 to 68.9)
Difference‡		6.8 (−9.3 to 22.9)		−2.1 (−21.3 to 17.2)

* The intervention lasted 9 months and was followed by a 3-month nonintervention period. ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker.
† Based on multiple imputation.
‡ Differences are reported in percentage points.

Table 3. **Emergency Department Visits and Hospitalizations***

Variable	Emergency Department Visits		Hospital Admissions		Combined Outcome	
	Intervention Group (n = 122)	Usual Care Group (n = 192)	Intervention Group (n = 122)	Usual Care Group (n = 192)	Intervention Group (n = 122)	Usual Care Group (n = 192)
All causes						
Mean (SD), n	2.16 (3.31)	2.68 (4.87)	0.78 (1.66)	0.97 (1.78)	2.94 (4.69)	3.65 (6.26)
Median (IQR), n	1 (0–3)	1 (0–3)	0 (0–1)	0 (0–1)	1 (0–3)	1.5 (0–4)
IRR (95% CI)†	0.82 (0.70–0.95)		0.81 (0.64–1.04)		0.82 (0.72–0.93)	
Cardiovascular						
Mean (SD), n	0.57 (1.39)	0.65 (1.63)	0.31 (0.86)	0.37 (0.91)	0.61 (1.72)	0.67 (1.95)
IRR (95% CI)‡	0.94 (0.51–1.73)		0.86 (0.45–1.63)		0.96 (0.48–1.91)	
Heart failure						
Mean (SD), n	0.30 (1.03)	0.30 (1.27)	0.11 (0.46)	0.15 (0.58)	0.40 (1.47)	0.44 (1.79)
IRR (95% CI)‡	1.09 (0.42–2.87)		0.77 (0.28–2.10)		1.00 (0.36–2.77)	

* IQR = interquartile range; IRR = incidence rate ratio.
† Using log-linear regression based on Poisson distribution.
‡ Using log-linear regression based on negative binomial distribution.

$205 per patient (**Appendix Table 3**, available at www.annals.org). Outpatient health care was $886 lower for patients in the intervention group (CI, −$2289 to $660) and was lower across all cost categories except drugs. Moreover, the cost of inpatient health care was $2277 less in the intervention group (CI, −$6329 to $1225). The mean difference in the overall cost of health care was $3165 lower in the intervention group (CI, −$7800 to $1138). Considering the costs of development and implementation, the intervention saved $2960 per patient (CI, −$7603 to $1338). However, no cost comparisons between groups were statistically significant because of the large variability in costs.

Adverse Drug Events and Medication Errors

Adverse drug events and medication errors did not statistically differ between groups. In the usual care group, 91 of 192 patients (47.4%) had an adverse event or medication error compared with 42 of 112 patients (37.5%) in the intervention group (chi-square = 2.81; P = 0.094). The between-group rates of these events were not statistically significant (P = 0.108).

DISCUSSION

The pharmacist intervention improved adherence to cardiovascular medications, including the proportion of medications taken, the reliability of scheduling these medications, and the amounts of medications refilled. However, the effects of the intervention on taking and scheduling adherence observed during the 9-month active intervention period dissipated in the 3-month postintervention period. Patients in the intervention group had fewer exacerbations requiring emergency room visits and hospital care and reported greater satisfaction with pharmacist services than did patients receiving usual care. Costs of care were lower and improvements in disease-specific quality of life were greater in the intervention group but were not statistically significant. With respect to costs, as more patients receive the intervention, the intervention development costs become negligible and the overall cost savings per patient approaches $3000. Indeed, the return on investment in our study is $14 for every dollar spent on the intervention, which contrasts greatly from the return on investment of $6.5 for every dollar spent in a recent meta-analysis of more intensive postdischarge interventions in older adults with heart failure (40).

We searched MEDLINE, available adherence bibliographies, and references from English-language publications of trials of similar pharmacist interventions for adults with heart failure up to December 2006. We found that previous randomized, controlled trials of pharmacist involvement in heart failure medication management programs have been encouraging. Gattis and colleagues (41) assessed how all-cause mortality and hospital admissions were affected by adding a clinical pharmacist to a multidisciplinary heart failure management team at a cardiology referral clinic. Similar to our intervention, the pharmacist in Gattis and colleagues' study conducted an initial evaluation of medication use and patient education, provided recommendations to patients' physicians, and performed follow-up monitoring by telephone for 6 months. A special effort was made to ensure that patients received the dosage of ACE inhibitor that is supported by heart failure guidelines. Compared with the usual care group, the intervention group had more patients receiving recommended ACE inhibitor dosages and fewer cardiovascular events. Although the authors used a questionnaire to determine self-reported adherence, they did not report these data. Health-related quality of life, patient satisfaction, and the costs of health care were not measured in the study. Tsuyuki and colleagues (42) also targeted ACE inhibitors in their 10-center trial of a pharmacist or nurse postdischarge intervention involving patient education, diaries, and adherence

support. They found a reduction in cardiovascular emergency department use between the intervention and usual care groups, but differences in refill adherence were not statistically significant. Bouvy and colleagues (43) studied a pharmacist intervention on treatment gaps in diuretic adherence, as measured by using electronic monitors. The intervention group had fewer missed diuretic days than the usual care group, but the groups did not statistically differ in other outcomes. Goodyer and colleagues (44) studied elderly patients receiving a 3-month intensive in-home medication counseling program. Adherence (measured by pill count) improved by 32% in the intervention group and remained unchanged in the control group. Exercise performance improved from baseline in the intervention group but worsened in the control group. Two additional small trials of pharmacist interventions for patients with heart failure (45, 46) were encouraging but had flaws in their design, execution, or both. These generally favorable results of pharmacist interventions are consistent with those of several other recent reports of multidisciplinary interventions, most of which promoted treatment adherence.

Multidisciplinary heart failure management programs that reduced hospital readmissions were more likely to include an inpatient component of care, patient education, self-care support, improvements to the medical regimen, and processes to identify and manage clinical exacerbation (47). These programs differed in intervention intensity, the personnel delivering the intervention, the type of intervention (telephone or personal contact), and complexity (48). Generally, multidisciplinary programs were more intense and comprehensive than our pharmacist intervention. Advanced practice nurses who specialize in disease management and work closely with a physician have been at the core of several of these programs (49, 50). Medication components of these programs often include verbal instruction and written support, but their descriptions are often vague in intensity, timing, method of delivery, and targeted health literacy level.

Although some programs involved a pharmacist (51–53), we are unaware of any that were managed from a pharmacy by a pharmacist who dispensed medications and provided other helpful functions. Because pharmacotherapy is central to the management of heart failure, almost all management programs promoted appropriate use of medications and adherence. However, only some programs measured adherence (49, 50). The pharmacist in our study dispensed medications to patients in the intervention group with tailored medication instructions that emphasized the importance of adherence to physicians' prescriptions. The pharmacist contacted physicians and nurses as needed, but most core functions were derived from the pharmacist's work with the patients. Overall, however, our intervention by a trained dispensing pharmacist seems to be much less comprehensive and less intense than previous interventions led by nurses or pharmacists. Nonetheless, the improvements in treatment adherence and modest reductions in health care use and costs that resulted from our intervention could be a worthwhile complement to existing multidisciplinary programs that lack such a pharmacist component (54).

Our study has several limitations. First, patients were recruited from a health center that serves a predominantly indigent population. Second, to ascertain adherence, we required patients to use electronic monitor containers and excluded patients who used special pill box adherence aids. Third, the intervention was delivered by a single pharmacist and precludes study of other factors, such as pharmacist attitudes or behaviors, that may have promoted delivery of the intervention. These factors may limit the generalizability of our findings. Finally, because the intervention had several components, such as verbal counseling and written materials, that were aimed at persons with low health literacy, we could not attribute intervention effects to any single component.

In conclusion, we found that our pharmacy-based intervention for outpatients with heart failure improved adherence to cardiovascular medications and decreased health care use. Because the salutary effects on adherence quickly dissipated when the intervention ended, continued intervention is probably necessary. If these study results are confirmed in other health care settings, policymakers might consider emphasizing the importance of pharmacists in promoting medication adherence for the reduction in health care use and associated costs of chronic diseases, such as heart failure.

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Appendix Table 1. **Pharmacist's Intervention Protocol***

Problem Category	Problem	Solutions
Low medication adherence	Suspect patient not taking medications as prescribed	Show the patient that you care. Discuss low medication adherence with the patient and determine reason. Identify a reason for the problem and solve it with the patient by using 1 of the interventions listed below: Identify forms of medications that could simplify the regimen (e.g., sustained-release, reduced frequency). Determine whether patient is complicating regimen with over-the-counter and herbal drugs. If drug might not be needed, ask physician whether it can be discontinued. Contact patient's physician to help reinforce with a positive message about the importance of medications and to reinforce pharmacist's plan.
Low MEMS adherence (unavailable at baseline)	Suspect patient misses doses or has erratic timing of doses	Examine whether drug was taken and the timing of dosing or missed doses. Is there a good reason for the pattern of dosing (e.g., too busy at work)? Show patient MEMS plot to determine reason for missing doses. Engage patient in problem solving to find a way to resolve.
Low medication adherence by self-report (available at baseline)	Suspect patient not taking medications as prescribed	Because the patient knows that there is a problem, discuss directly with patient. Engage patient in problem solving about way to resolve. Determine whether there is an "intelligent" reason for low adherence, such as drug allergy or an intolerable side effect, and make recommendations to physician.
Low refill adherence (available at baseline)	Patient misses refills or has erratic timing of refills	Patients sometimes do not pick up refills because they cannot afford their medications any longer. If the patient is required to pay, can the patient afford it? Consider referral to financial services counselor. Consider a special drug plan for indigent person. The patient may have a new drug source. Ask patient whether they are getting medications elsewhere. Patient may be stretching his or her quantities by taking fewer pills or a smaller dosage. Inspect MEMS plot to determine whether doses were skipped. If not, ask where patient is getting medications. If MEMS and refill adherence agree, determine reasons for not picking up refills.
Knowledge	Lack of understanding of heart failure concepts as they relate to diet and drug therapy	Explain fundamentals of heart failure and its management to patient in terms he or she can understand. Provide patient education materials as needed to clarify concepts.
	Lack of understanding of the relationship of hypertension or diabetes management to heart failure management	Explain how poor management of hypertension and diabetes contribute to worsening of heart failure. Provide patient with the handout on the importance of blood pressure medicines† or importance of diabetes medicines‡.
	Lack of understanding of drug-specific information	Explain in terms patient can understand the rationale for the use of the icon system, how various icons belong to a specific medication type, and how these icons and colors map to the patient education materials. Use the approach espoused by Lorig (55). Namely, tell patients what you want them to do, show them how to do it, provide written instructions, and ask them how they plan to do it.
	Needs further drug-specific information	Explain in terms patient can understand the rationale for needing a specific medication and its relationship to the other medications. Provide patient with appropriate handout.
	Needs diet-specific instruction, especially relating to low-sodium diets	Ask patient about salty foods he or she eats and verbally provide patient with the names of alternatives that contain less salt. Provide patient with "Healthy Heart"§ handout.
Beliefs	Patient does not believe he or she needs the medication Lack of perceived self-efficacy	Provide verbal and written education materials. Discuss patient's beliefs with his or her physician. Work with the patient to help him or her better manage the drug regimen. Build his or her confidence in medication management routines.
Expectations	Patient's needs are not being met according to data from the Expectations Questionnaire	Discuss patient's expectations with him or her. Determine whether drug-related expectations are realistic (e.g., desire for a prescription for unwarranted medications). Refer disease management expectations to primary care physician and nurse.

Appendix Table 1—**Continued**

Problem Category	Problem	Solutions
Prescription-taking skills	Pharmacist's assessment suggests an inability to read instructions on prescription label	Literacy problem: Review prescription-specific icon system on each medication-specific pamphlet. Explain medication administration timeline. Vision problem: Find a font size that the patient can adequately read and use it on the medication-specific pamphlet. Blind: Use raised lettering or Braille on prescription lids and container.
	Pharmacist's assessment suggests an inability to comprehend instructions	Review prescription-specific icon system on each medication-specific pamphlet. Explain medication administration timeline on the medication pamphlets.
Communication skills	Patient finds it difficult discussing problems with his or her physician	Determine gaps in patient's knowledge and treatment plan and provide patient with a list of questions to ask the physician by phone or at his or her next visit.
	Patient forgets what his or her physician says	Ask patient to have physician or nurse write down his or her instructions. If the patient forgets or loses the instruction list, encourage him or her to call physician.
	Patient does not agree with physician's treatment	Medicine not effective: Encourage patient to discuss alternative treatments with his or her physician. Side effects: Encourage patient to discuss problem with physician. Pharmacist should call physician to describe the side effect and determine alternative treatment. Other: Encourage patient to work closely with his or her physician and explain the reason for his or her disagreement with the physician's choice of treatments. Pharmacist should call the patient's physician to explain the situation depending on the nature and magnitude of the problem.
Supervision	Patient lives alone and has no one to supervise self-administration of medications	Provide motivation for patient to take medications and use aids to improve adherence and reminders. Call patient to follow up and show him or her that you care that he or she takes his or her medication. Coach patient on taking his or her medications. If no improvement, contact physician and possibly social services.
Perceived health	Patient does not realize the severity of his or her illness	Establish the severity of the disease. Educate patient about the importance of treating heart failure and associated comorbid conditions to prevent or slow the progression of the disease. Provide disease- and drug-specific education pamphlets.
	Patient with mild disease is frightened about his or her fate	Provide disease- and drug-specific education pamphlets. Be optimistic with patient. Encourage patient to discuss his or her feelings with his or her physician and nurse.
Cognitive function	Patient does not remember to take medications	Provide reminders, such as patient-specific calendar to mark when they take medications.
	Problem with source monitoring	Provide reminders, such as patient-specific calendar to mark when they take medications.
	Problem with prospective memory	Identify a daily activity or cue that the patient does regularly at about the time they should take medications and explain to the patient to take medications at this time. Call the patient by telephone at the time of the cue for the first day or 2 to remind the patient and get the patient in the habit of using the cue. Use alarm clock or microwave oven alarm to remember next dose.
Coping	Patient is not coping with his or her medical problems or treatment	Provide disease- and drug-specific education pamphlets. Be optimistic with patient. Encourage patient to discuss his or her feelings with their physician and nurse. Share this information with the patient's physician and nurse.
Poor vision		Explain icon-based education materials. Refer to eye clinic.
Poor hearing		Use hearing amplifier to educate patient and explain icon-based education materials.

* Medication Event Monitoring System (MEMS) prescription container lids (AARDEX Ltd., Zug, Switzerland).
† Available at www.nhlbi.nih.gov/hbp/index.html (accessed on 4 April 2007).
‡ Available at http://diabetes.niddk.nih.gov/dm/pubs/complications_heart/index.htm (accessed on 4 April 2007).
§ Available at www.pharmacy.unc.edu/cpop (accessed on 4 April 2007).

Appendix Table 2. **Sensitivity Analysis of Taking and Scheduling Adherence during the Intervention Period**

Sensitivity Analysis	Outcomes at 9 Months				Difference (95% CI), *percentage points*	*P* Value
	Ratio of Adherent–Nonadherent Noncompleters, *n:n**		Mean Adherence (SD), %			
	Intervention Group (*n* = 122)	Usual Care Group (*n* = 192)	Intervention Group (*n* = 122)	Usual Care Group (*n* = 192)		
Overall taking adherence scenario						
1	1:1	1:1	78.8 (19.6)	67.1 (27.8)	11.7 (6.0 to 17.4)	<0.001
2	1:1	1:2	78.8 (19.6)	66.5 (27.9)	12.3 (6.6 to 18.0)	<0.001
3	1:1	2:1	78.8 (19.6)	68.0 (27.6)	10.8 (5.2 to 16.5)	<0.001
4	1:2	1:1	77.8 (20.6)	67.1 (27.8)	10.7 (4.9 to 16.4)	<0.001
5	1:2	1:2	77.8 (20.6)	66.5 (27.9)	11.3 (5.5 to 17.1)	<0.001
6	1:2	2:1	77.8 (20.6)	68.0 (27.6)	9.8 (4.1 to 15.6)	<0.001
7	2:1	1:1	79.5 (19.4)	67.1 (27.8)	12.4 (6.7 to 18.1)	<0.001
8	2:1	1:2	79.5 (19.4)	66.5 (27.9)	13.0 (7.3 to 18.7)	<0.001
9	2:1	2:1	79.5 (19.4)	68.0 (27.6)	11.5 (5.9 to 17.2)	<0.001
Overall scheduling adherence scenario						
1	1:1	1:1	54.6 (22.3)	48.0 (44.4)	6.6 (1.1 to 12.0)	0.019
2	1:1	1:2	54.6 (22.3)	47.5 (24.7)	7.1 (1.7 to 12.5)	0.010
3	1:1	2:1	54.6 (22.3)	48.7 (25.6)	5.9 (0.3 to 11.4)	0.039
4	1:2	1:1	53.9 (22.0)	48.0 (44.4)	5.9 (0.5 to 11.4)	0.034
5	1:2	1:2	53.9 (22.0)	47.5 (24.7)	6.4 (1.1 to 11.8)	0.019
6	1:2	2:1	53.9 (22.0)	48.7 (25.6)	5.2 (−0.3 to 10.8)	0.064
7	2:1	1:1	55.5 (22.6)	48.0 (44.4)	7.5 (2.0 to 13.0)	0.008
8	2:1	1:2	55.5 (22.6)	47.5 (24.7)	8.0 (2.6 to 13.5)	0.004
9	2:1	2:1	55.5 (22.6)	48.7 (25.6)	6.8 (1.2 to 12.4)	0.017

* Noncompleters are individuals with missing data because they discontinued their participation in the study or lost their electronic medication container monitor lids. The noncompleter ratio is the ratio of adherent versus nonadherent patients with missing data. For example, scenario 1 indicates that the ratio of adherent and nonadherent patients is the same in those who had missing information in the intervention and usual care groups. Scenario 2 assumes that the ratio of adherent to nonadherent patients with missing data is equal (1:1) in the intervention group but that there are twice as many nonadherent patients as adherent patients (1:2) among the noncompleters in the usual care group.

Appendix Table 3. Mean Patient Costs*

Variable	Cost in the Intervention Group (n = 122), $	Cost in the Control Group (n = 192), $	Difference (95% CI), $
Intervention costs			
Fixed cost per patient†	40 (0)	–	–
Variable cost per patient	165 (86)	–	–
Total intervention cost	205 (86)	–	–
Outpatient costs			
Physician cost	413 (387)	495 (469)	−82 (−176 to 15)
Procedure cost	679 (1767)	877 (1367)	−198 (−479 to 323)
Facility cost	3091 (3641)	3469 (3884)	−378 (−1179 to 515)
Test cost	836 (2302)	1101 (1860)	−265 (−633 to 445)
Treatment cost	131 (473)	210 (482)	−79 (−172 to 46)
Drug cost	334 (937)	220 (618)	113 (−46 to 335)
Total outpatient cost	5483 (6434)	6373 (6501)	−889 (−2289 to 660)
Inpatient costs			
Facility cost	1761 (3906)	2005 (4244)	−244 (−1120 to 699)
ICU cost	1106 (4149)	1766 (6890)	−659 (−2087 to 387)
Pharmacy cost	795 (2161)	1417 (4792)	−623 (−1593 to 15)
Test cost	552 (1311)	747 (1755)	−195 (−544 to 138)
Rehabilitation cost	504 (2117)	642 (2329)	−139 (−622 to 395)
Physician cost	833 (2124)	1249 (3673)	−416 (−1206 to 111)
Total inpatient cost	5550 (13 847)	7827 (20 413)	−2277 (−6329 to 1225)
Total costs	11 034 (17 211)	14 199 (23 672)	−3165 (7800 to 1138)
Total costs with intervention	11 239 (17 215)	14 199 (23 672)	−2960 (−7603 to 1338)

* Values are expressed as means (SDs), unless otherwise indicated. ICU = intensive care unit.
† Fixed costs per patient were the development costs of the intervention divided by the number of patients. This amount decreases as the number of patients receiving the intervention increases.