

Reduction in Heart Failure Events by the Addition of a Clinical Pharmacist to the Heart Failure Management Team

Results of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study

Wendy A. Gattis, PharmD, BCPS; Vic Hasselblad, PhD; David J. Whellan, MD; Christopher M. O'Connor, MD

Background: The multidisciplinary approach to managing heart failure has been shown to improve outcomes. The role of a clinical pharmacist in treating heart failure has not been evaluated.

Methods: One hundred eighty-one patients with heart failure and left ventricular dysfunction (ejection fraction <45) undergoing evaluation in clinic were randomized to an intervention or a control group. Patients in the intervention group received clinical pharmacist evaluation, which included medication evaluation, therapeutic recommendations to the attending physician, patient education, and follow-up telemonitoring. The control group received usual care. The primary end point was combined all-cause mortality and heart failure clinical events. All clinical events were adjudicated by a blinded end point committee.

Results: Baseline characteristics were similar except for slightly higher age in the intervention group.

Median follow-up was 6 months. All-cause mortality and heart failure events were significantly lower in the intervention group compared with the control group (4 vs 16; $P = .005$). In addition, patients in the intervention group received higher angiotensin-converting enzyme inhibitor doses as reflected by the median fraction of target reached (25th and 75th percentiles), 1.0 (0.5 and 1) and 0.5 (0.1875 and 1) in the intervention and control groups, respectively ($P < .001$). The use of other vasodilators in angiotensin-converting enzyme inhibitor-intolerant patients was higher in the intervention group (75% vs 26%; $P = .02$).

Conclusions: Outcomes in heart failure can be improved with a clinical pharmacist as a member of the multidisciplinary heart failure team. This observation may be due to higher doses of angiotensin-converting enzyme inhibitors and/or closer follow-up.

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HEART FAILURE is a highly prevalent illness, affecting more than 3 million Americans. The incidence of heart failure is increasing, with 400 000 new cases diagnosed annually.^{1,2} The prevalence of heart failure exponentially increases with advanced age.^{3,4} Not surprisingly, heart failure is the most common discharge diagnosis among patients older than 65 years.⁵ Rehospitalizations for heart failure are also common. Ninety-day readmission rates as high as 47% have been reported.⁶ Although many causes of heart failure exacerbations requiring hospitalization can be identified, medication and dietary non-compliance have been reported as contributing factors in up to 33% of hospitalized patients.^{6,7}

Recent studies have evaluated the multidisciplinary approach to managing heart failure in an effort to reduce these

readmissions.⁸⁻¹² The focus of the intervention has included patient education, discharge planning, medication regimen reviews, home health care, dietary instruction, and telephone follow-up provided by nurses, dietitians, social workers, and physicians. Although 1 study used clinical pharmacy services to assess compliance,¹⁰ to our knowledge no direct involvement in patient care by a clinical pharmacist has been reported.

The objective of the Pharmacist in Heart Failure Assessment Recommendation and Monitoring (PHARM) Study was to evaluate the effect of a clinical pharmacist on outcomes in outpatients with heart failure. The primary end point was the composite of all-cause mortality and nonfatal heart failure events (emergency department visits or hospitalizations for heart failure). Use and dose of angiotensin-converting enzyme (ACE) inhibitors prescribed were evaluated as secondary objectives.

From the Division of Cardiology, Department of Medicine, Duke University Medical Center, and the Duke Clinical Research Institute, Durham, NC.

SUBJECTS AND METHODS

The study was approved by the Duke University Medical Center Institutional Review Board, Durham, NC. All patients undergoing evaluation in a general cardiology faculty clinic with a diagnosis of heart failure based on signs and symptoms of heart failure and left ventricular ejection fraction of less than 45% were eligible for participation. Patients were excluded from participation if they were not expected to survive for 6 months because of a terminal illness, if they were currently participating in an investigational drug trial, if their primary residence was a skilled nursing facility, or if they had marked dementia or another psychological disorder that prevented participation in patient education and follow-up. Eligible patients were asked to provide informed consent. After consent was obtained, patients were randomized according to a computer-generated randomization scheme to pharmacist intervention or usual care. Patients in both groups provided verbal responses to an identical set of the following 10 questions regarding their current drug therapy to assess the prescribed regimen, compliance, and adverse effects:

1. What has your physician prescribed this medication for?
2. What dose of the medication has your physician prescribed?
3. How many times during the day did your physician prescribe the medication?
4. How many times during the day do you take the medication?
5. What times of day do you take the medication? Do you take your medication at the same time every day?
6. How do you take the medication in relation to meals? How do you take the medication in relation to your other medicines?
7. How many times a week do you miss a dose of the medication?
8. What do you do if you forget a dose of the medication?
9. Do you ever stop taking a medication or change the dose without your physician's instruction? If so, what caused you to stop or change the medicine?
10. How does the cost of your medication affect your ability to take it?

Individualized questions pertaining to the patients' heart failure status and histories were asked as well to assess symptoms and response to therapy. For patients in the intervention group, the clinical pharmacist discussed the patient's case and verbally provided therapeutic recommendations regarding optimization of therapy to the attending physician. Recommendations were based on information collected from the patient interview, history, and the patient's current drug regimen. Focus was placed on optimizing heart failure therapy (including use of ACE inhibitors, increase of ACE inhibitor dose to target, and use of alternative vasodilators in ACE-inhibitor-intolerant patients), avoiding digoxin toxicity, avoiding contraindicated drugs or drug interactions, and recommending other medication changes as indicated in individual patients. The clinical pharmacist then discussed changes made in drug therapy with the patient. The pharmacist explained the purpose of each drug and the importance of adhering to the prescribed regimen. Directions for use of each drug and potential adverse effects were discussed in detail and were provided in written form by the clinical pharmacist on a medication calendar. Patients were given the opportunity to ask the pharmacist questions regarding their drug therapy and were provided with a telephone number to contact the clinical pharmacist should additional questions or problems arise. The clinical pharmacist provided telephone follow-up at 2, 12, and 24 weeks after the initial clinic visit to identify problems with drug therapy, to answer drug-related questions, and to identify the occurrence of clinical events. If patients indicated continuing or worsening symptoms, the pharmacist recommended that the patient contact their physician for further evaluation. The pharmacist also contacted the physician to discuss such cases. Changes made in the medical regimen based on the physician-pharmacist interaction were discussed with the patient by the clinical pharmacist.

The control group received usual care. The pharmacist provided no recommendations regarding drug therapy to the attending physician and provided no patient education in this group. Patient assessment and education were provided by the attending physician and/or physician assistant or nurse practitioner. The pharmacist contacted the

RESULTS

A total of 1568 patients underwent evaluation in clinic and screening for participation from October 1, 1996, to July 31, 1997. Of these, 192 satisfied the enrollment criteria. Eleven patients declined participation. One hundred eighty-one patients were enrolled in the study (**Figure 1**). Baseline characteristics were similar between groups, with the exception of median age, which was slightly higher in the intervention group (**Table 1**). The median follow-up was 6 months.

The effect of clinical pharmacist intervention on the primary end point of all-cause mortality and nonfatal heart failure events is illustrated in **Figure 2**. Four events occurred in the intervention group compared with 16 events in the control group (odds ratio [OR], 0.22; 95% confidence interval [CI], 0.07-0.65; $P = .005$). The effect was largely due to a reduction in hospitaliza-

tion or emergency department visits for heart failure, as the effect on total mortality was small and not statistically significant (**Table 2**). The Cox proportional hazards model demonstrated that the intervention was significant ($P = .02$) after adjustment for age and other prognostically important variables including ischemic cause and ejection fraction.

Patients in the intervention group were closer to target ACE inhibitor dose at 6-month follow-up as reflected by the median fraction of target dose (25th and 75th percentiles) reached, ie, 1.0 (0.5 and 1) for the intervention group and 0.5 (0.1875 and 1) for the control group ($P < .001$). No difference in overall ACE inhibitor use was observed between groups (**Table 3**). Of the patients not receiving ACE inhibitors, 75% of the intervention group were receiving alternative vasodilator therapy at follow-up compared with 26% of the control group ($P = .02$).

control group by telephone at 12 and 24 weeks after the enrollment visit to identify clinical events. Neither patients nor physicians were told directly of the treatment assignment, although the direct-intervention nature of the study prevented complete blinding.

STATISTICAL METHODS

Dichotomous outcomes were summarized in 2×2 tables and were analyzed using the likelihood ratio χ^2 test.¹³ Continuous variables were presented as medians along with 25th and 75th percentiles. These variables were tested using a Wilcoxon rank sum test.¹⁴ The response variables for the primary end point (death, hospitalization, or emergency department visit for heart failure) were analyzed using a Cox proportional hazards model.^{13,14}

DATA COLLECTION

Demographic and clinical data were obtained from the patients' medical records (medical history, demographics) and from results of clinical evaluation on the day of enrollment (heart failure signs and symptoms, laboratory values, drug therapy). Data were entered into a database designed specifically for the study using commercially available software (Microsoft Access 7.0; Microsoft Corp, Seattle, Wash). Clinical events and current drug therapy were documented on follow-up data collection forms during telephone follow-up or return visits. The intervention group received telephone follow-up at 2, 12, and 24 weeks. Patients were asked if they had been to the emergency department or the hospital for any reason. The Duke University Medical Center database was queried for hospitalizations or emergency department visits for all patients. Patient report and database query were used to identify Duke University Medical Center admissions or emergency visits. For those patients admitted to outside hospitals, patient report was the only method to identify clinical events. Clinical events in the control group were evaluated during follow-up telephone calls at 12 and 24 weeks. The Duke University Medical Center database was also queried to identify clinical events for these patients, and patients were asked

during telephone follow-up if they had been to the emergency department or hospital for any reason.

Medical records documenting events in both groups were obtained for review by the clinical events committee. Clinical events were adjudicated by a blinded physician clinical events committee using standard adjudication forms. Death was classified by cause (pump failure, sudden cardiac death, fatal myocardial infarction, stroke, or noncardiac cause). Reasons for hospitalization or emergency department visits were classified as cardiovascular (heart failure, arrhythmia, acute coronary syndrome [unstable angina or myocardial infarction], cerebrovascular accident, transient ischemic attack, or nonemergent or elective procedures) or noncardiovascular.

END POINT DEFINITIONS

Heart failure hospitalization was hospitalization primarily due to volume overload or other symptoms of heart failure. *Arrhythmia hospitalization* was hospitalization primarily due to underlying arrhythmia (atrial fibrillation, ventricular tachycardia, etc). *Acute coronary syndrome hospitalization* was hospitalization for unstable angina or myocardial infarction. *Nonemergent or elective hospitalization* was hospitalization for procedures including elective or nonemergent cardiac catheterization, cardioversion or other electrophysiologic procedure, or elective noncardiac procedures.

Medication use was evaluated at baseline enrollment and at each follow-up encounter. Patients who were not receiving ACE inhibitors were classified by the reason why no ACE inhibitor was prescribed. The dose of ACE inhibitor was also obtained and converted to a fraction of the target dose. *Target doses* were defined as those doses evaluated in randomized controlled clinical trials, or the estimated equivalent in the case of those agents that have not been studied. Target doses were as follows: 50 mg 3 times per day for captopril, 10 mg twice a day for enalapril maleate, 20 mg/d for lisinopril, 5 mg twice a day for ramipril, 40 mg/d for quinapril hydrochloride, and 40 mg/d for benazepril hydrochloride. A dose of captopril, 25 mg 3 times a day, was assigned a value of 0.5 for the fraction of the target dose.

COMMENT

The benefits of a multidisciplinary team on the management of heart failure have been clearly demonstrated by Rich et al.⁹ In their study, 282 elderly patients with heart failure admitted to the hospital with risk factors for readmission were randomized to a multidisciplinary intervention or to usual care. Although a significant reduction in 90-day survival without readmission (the primary end point) was not observed, a significant reduction in readmission rates was detected (42% for control group vs 29% for intervention group; $P = .03$). The intervention was provided by a multidisciplinary group of individuals including nurses, social workers, dietitians, and physicians and focused on patients in the hospital setting.

Most patients with heart failure are treated as outpatients, and the care of these patients is challenging. Less time is available for outpatient evaluations, and much

more reliance is placed on telemonitoring and contact between clinic visits. Thus, the outpatient clinic setting is an ideal environment to implement a multidisciplinary team care approach. Little is known about the impact of a multidisciplinary team with a pharmacist in this setting.

Pharmacists are recognized as important members of the health care team. The ability of clinical pharmacists to assist in the management of a variety of disease states, including hypertension, diabetes mellitus, hyperlipidemia, and anticoagulation therapy, has been documented.¹⁵⁻²⁰ However, to our knowledge, their role as health care providers among patients with heart failure has not been evaluated.

The role of the pharmacist in the setting of heart failure is multifactorial.¹⁸ Considering the syndrome of heart failure alone, patients are likely to be receiving a minimum of 4 medications. Because most patients with heart

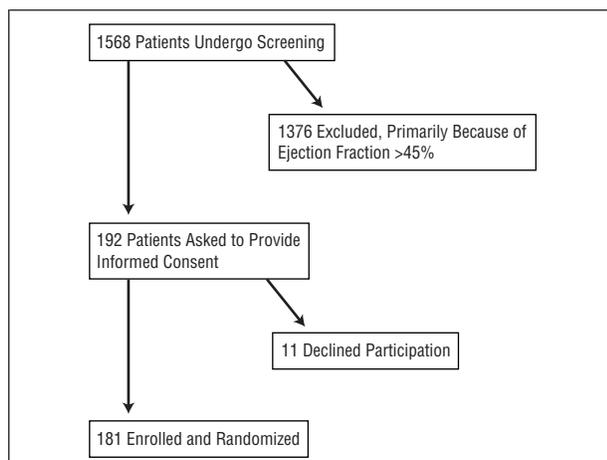


Figure 1. Schematic of patient screening and enrollment.

	Intervention (n = 90)	Control (n = 91)
Age, y	71.5 (60, 77)	63.0 (55, 72)
Male, No. (%)	62 (69)	61 (67)
White, No. (%)	72 (80)	72 (79)
Cause, No. (%)		
Ischemic	72 (80)	70 (77)
Nonischemic	18 (20)	21 (23)
NYHA class, No. (%)		
I	12 (13)	11 (12)
II	47 (52)	51 (56)
III	28 (31)	26 (29)
IV	3 (3)	3 (3)
Ejection fraction, %	30 (20, 40)	30 (20, 37.5)
Systolic blood pressure, mm Hg	124 (110, 150)	122 (110, 137.5)
Diastolic blood pressure, mm Hg	70 (61.5, 80)	70 (61, 76)
Serum creatinine, $\mu\text{mol/L}$ (mg/dL)	91.5 (76.3, 114.4) (1.0 [0.9, 1.3])	76.3 (68.6, 95.3) (0.9 [0.8, 1.1])
No. of medications	6.5 (5, 8)	6 (4.5, 8)

* Values are given as median (25th, 75th percentiles) unless otherwise indicated. Percentages have been rounded and may not total 100. NYHA indicates New York Heart Association.

failure have ischemic heart disease and other concomitant diseases, this figure quickly may approach 10 or more medications. The potential for drug interactions, toxic effects, or other adverse reactions increases dramatically as the number of prescribed drugs increases.²¹ The education and training of clinical pharmacists is unique among health care professionals. This background enables them to review drug regimens for interactions and appropriate dosing based on pharmacokinetics and patient-specific factors, including age, renal function, hepatic function, and other medications.

Clinical pharmacists knowledgeable in the evidence-based treatment of heart failure can assist the physician in the selection and optimization of appropriate and cost-effective drug therapy. In our study, intervention patients were more likely to be receiving target ACE inhibitor doses. This finding suggests that the successful management of heart failure is multifactorial and en-

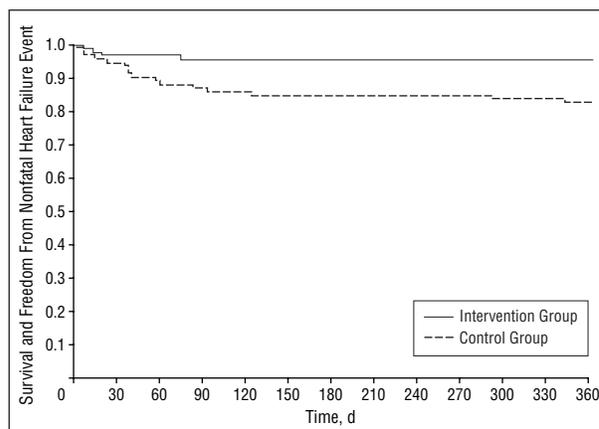


Figure 2. Kaplan-Meier curves for all-cause mortality and nonfatal heart failure events ($P = .005$).

compasses a wide variety of interventions, including diagnostic, therapeutic, pharmacological, and lifestyle modifications. The availability of a multidisciplinary team including physicians, pharmacists, nurses, nutritionists, physical therapists, physician extenders, midlevel health care providers, health care managers, and social workers is vitally important.

Pharmacists may play a role in patient follow-up and monitoring of drug therapy. Close follow-up of the patient with heart failure is increasingly important, especially when instituting drug therapy such as β -adrenergic blockade.²² In addition, new medications are often initiated by other practitioners between clinic visits, and patients often self-treat symptoms with nonprescription medications. Close follow-up allows continual evaluation of drug therapy to screen for response to therapy, drug interactions, or contraindicated medications.

Finally, pharmacists have an important role as patient educators. Patient education is a vital component of heart failure management and reinforces the importance of medication adherence. Medication nonadherence is a common cause of hospital admission for heart failure; thus, the importance of compliance cannot be overemphasized and should be reiterated by each member of the health care team.^{6,7,23,24}

A reduction in hospital readmissions has been reported with a multidisciplinary team consisting of physicians, nurses, social workers, and dietitians knowledgeable in the treatment of heart failure.⁹ To our knowledge, this study is the first to evaluate and to demonstrate a reduction in clinical events when a pharmacist is incorporated in the heart failure team. Clinical pharmacists, as well as each health care professional, contribute a unique expertise to patient care based on their background and training. The findings of this and previously published studies suggest that optimal care of the patient with heart failure is achieved with the use of a multidisciplinary team, with each provider contributing to improved patient outcomes. Our results demonstrate the value of incorporating pharmacists in addition to the other vital members of the heart failure management team (Figure 3).

The observed reduction in hospitalization and death rates in our study may have occurred for several

Table 2. Clinical Events*

Event	No. of Events		OR (95% CI)	P
	Intervention Group (n = 90)	Control Group (n = 91)		
Nonfatal heart failure	1	11	0.08 (0.004-0.4)	.005
Other nonfatal cardiovascular		
Acute coronary syndrome	4	8		
Arrhythmia	2	3		
Other vascular events or stroke	1	1		
Total nonfatal cardiovascular	8	23	0.31 (0.13-0.69)	.004
All-cause mortality	3	5	0.59 (0.12-2.49)	.48
Heart failure	1	1		
Sudden cardiac death	2	3		
Noncardiovascular	0	1		
All-cause mortality and nonfatal heart failure†	4	16	0.22 (0.06-0.63)	.005
Nonemergent or elective procedures		
Admission for elective cardioversion	2	1		
Admission for elective cardiac catheterization	2	0		
Admission for elective electrophysiology procedure (other than cardioversion)	3	0		
Admission for noncardiac procedure	2	0		
Nonfatal noncardiovascular	9	7
Total	29	36	0.73 (0.39-1.33)	0.30

*OR indicates odds ratio; CI, confidence interval; and ellipses, number of events were too small to test.

†Primary end point of study.

Table 3. Use of ACE Inhibitors or Alternative Therapy*

	Intervention Group (n = 90)		Control Group (n = 91)		P†
	Baseline	Follow-up	Baseline	Follow-up	
Receiving ACE inhibitor, No. (%)	70 (78)	78 (87)	71 (78)	72 (79)	.18
Fraction of target ACE inhibitor dose‡	0.5 (0.125, 1)	1 (0.5, 1)	0.5 (0.125, 1)	0.5 (0.188, 1)	<.001
Reason for no ACE inhibitor§					
No reason	13 (65)	2 (17)	16 (80)	15 (79)	...
Hypotension	0	0	1 (5)	0	
Hyperkalemia	0	2 (17)	0	0	
Elevated serum creatinine level or renal artery stenosis	2 (10)	4 (33)	1 (5)	1 (5)	
Cough	5 (25)	4 (33)	2 (10)	3 (16)	
Alternative therapy	9 (45)	9 (75)	5 (25)	5 (26)	.02
Hydralazine hydrochloride or nitrates	3 (15)	5 (42)	2 (10)	1 (5)	
Losartan potassium	6 (30)	4 (33)	3 (15)	4 (21)	
No alternative therapy	11 (55)	3 (25)	15 (75)	14 (74)	...

*ACE indicates angiotensin-converting enzyme; ellipses, not calculated.

†Indicates difference between intervention and control group at follow-up.

‡Given as median (25th, 75th percentiles).

§For the intervention group, n = 20 at baseline, and n = 12 at follow-up; for the control group, n = 20 at baseline, and n = 19 at follow-up.

reasons. First, the patients in the intervention group had closer follow-up than the control group. In an earlier study by Weinberger et al,²⁵ however, hospital readmission and length of stay increased in chronically ill patients who received an intervention to increase access to primary care. One explanation for the increased event rate may be that the patients of Weinberger et al were severely ill, and of the patients with diagnoses of heart failure, 50% had New York Heart Association functional class III or IV heart failure. Conversely, the largest percentage of patients in our study had functional class II or III heart failure. Close follow-up in our population may have allowed for early detection of

signs and symptoms of volume overload. Findings suggestive of clinical instability by the clinical pharmacist during telephone follow-up could be reviewed quickly with a physician, and dose adjustments in diuretics or other drugs could be performed over the telephone, potentially aborting episodes of heart failure decompensation. Close surveillance by the clinical pharmacist also enabled early evidence of electrical instability or early progressive angina to be recognized such that the physician could be alerted, thereby avoiding emergent hospitalizations and allowing elective, nonemergent procedures to be conducted. Follow-up also provided opportunity for reevaluation of the medication regimen,

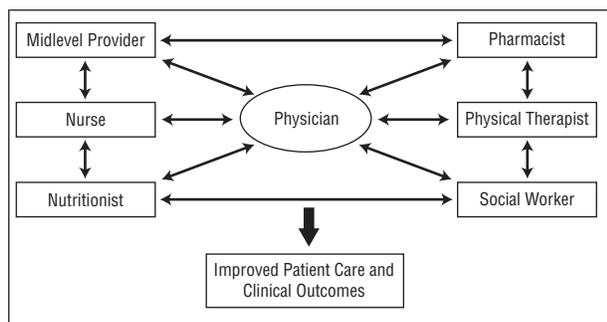


Figure 3. Schematic displaying the multidisciplinary heart failure team. The physician is the center of the team. The double-sided arrows represent the contributions and importance of communication between each team member. This approach has resulted in improved patient care and clinical outcomes.

such that new prescription or nonprescription drugs added since the last clinic visit could be screened for drug interactions or contraindications. Reinforcement of dietary sodium restriction and the importance of medication compliance also took place during follow-up telemonitoring. Each of these elements likely contributed to the significant reduction in death or heart failure clinical events observed in this study.

Another potential explanation for our observed reduction in hospitalization and death was the higher dose of prescribed ACE inhibitors in the intervention group. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial²⁶ studied more than 3000 patients to determine if a mortality difference existed between low- and high-dose lisinopril. No significant differences in all-cause mortality were observed between groups, but there was a significant reduction in the composite of death and all-cause hospitalizations and in hospitalizations for heart failure in the high-dose lisinopril group.

To our knowledge, our study is the first to evaluate a heart failure management program including a pharmacist in outpatients with mild to moderate heart failure. Although most patients in the study by Rich et al⁹ were in New York Heart Association class II, the patients were required to have risk factors for readmission to be eligible for the study. Thus, their study population likely consisted of patients with more advanced heart failure than ours. The higher event rate observed in the study by Rich et al⁹ would also support the more advanced nature of that population. Patients with advanced heart failure are more likely to be hospitalized; close follow-up in these patients by heart failure management programs has clearly proven beneficial in reducing hospital admissions.⁹ Event rates in patients with mild to moderate heart failure are generally lower; therefore, dramatic reductions in hospitalizations and other clinical events may not be apparent. Other important contributions of the multidisciplinary heart failure management program include optimizing medical therapy and intensive patient education, factors that may benefit significantly the patient with mild to moderate heart failure by slowing progression of left ventricular dysfunction.

There are several limitations of this study. First, the inability of the study to be completely blinded is a weakness. However, the nature of the intervention prohib-

ited such blinding. The study was randomized, and clinical events were adjudicated by a blinded end point committee. The acceptance rates of pharmacist recommendations were not evaluated because of the inconsistencies in obtaining the data. Data collection for evaluation of the secondary end point (ACE inhibitor dose) was slightly limited. Dose reductions due to adverse effects were not consistently captured. The location of the study was a referral clinic; thus, medication adjustments by the primary care physician and reasons for such adjustments were not consistent.

CONCLUSIONS

The results of this randomized trial suggest that clinical pharmacists appropriately trained in the management of heart failure are an important component of the multidisciplinary heart failure team and significantly contribute to the overall care of these patients. Pharmacists with a clinical expertise in the setting of heart failure are a valuable resource and should be incorporated as members of the health care team within this population.

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Reprints: Wendy A. Gattis, PharmD, BCPS, Duke University Medical Center, Division of Cardiology, Department of Medicine, Box 3356, Room 7401-A Duke North, Durham, NC 27710 (e-mail: gatti004@mc.duke.edu).

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