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Effect of Heart Failure Program on Cardiovascular Drug Utilization and Dosage in Patients with Chronic Heart Failure

TARIK M. RAMAHI, M.D., MARCELLA D. LONGO, M.D., KATE ROHLFS, R.N., NATALIE SHEYNBERG, M.D., PH.D.

Heart Failure and Transplant Cardiology Program, Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA

Summary

Background: Utilization and dosage of angiotensin-converting enzyme (ACE) inhibitors in patients with chronic heart failure (CHF) remain low. Recent data suggest that care of patients with CHF in specialized heart failure programs is associated with improved clinical outcomes.

Hypothesis: Specialized heart failure care is associated with better utilization and higher dose of cardiovascular drugs.

Methods: Data from 133 patients with CHF referred to a heart failure program were analyzed. Mean functional class 3.1 ± 0.5, left ventricular ejection fraction 19 ± 8. Utilization and doses of cardiovascular drugs were examined at initial evaluation and at last visit, after an average period of 17 ± 14 months. Hospitalization and survival data were determined.

Results: Utilization of ACE inhibitors and angiotensin-receptor blockers increased from 87 to 100% ($p < 0.001$). Average daily dose increased by 60%, from the equivalent of captopril 105 ± 78 mg to 167 ± 86 mg ($p < 0.001$). Utilization of the following drugs increased significantly: beta blockers (16–37%, $p < 0.001$), metolazone (10–23%, $p = 0.007$), spironolactone (1–36%, $p < 0.001$), amiodarone (7–15%, $p = 0.05$), hydralazine (1–9%, $p = 0.004$), and nitrates (20–33%, $p = 0.03$). One-year survival was 90%. The 3- and 6-month hospitalization rates for heart failure were 4 and 7%, and for all cardiovascular causes they were 6 and 11%, respectively.

Conclusions: Care of patients with CHF in a specialized heart failure program was associated with significant increase in the utilization and doses of all beneficial cardiovascular drugs, especially ACE inhibitors. It was also associated with excellent clinical outcomes.

A related editorial entitled "Specialized Heart Failure Centers—A Success or an Indicator of the Failure of Our Health Care Delivery System" by Pitt and Nicklas appears on page 881.

Key words: heart failure, drug utilization and doses, angiotensin-converting enzyme inhibitors

Introduction

Chronic heart failure (CHF) is a disease of high morbidity and mortality, accounting in the United States alone for more than 700,000 annual clinic visits, 800,000 hospital discharges, and contributing to or causing 250,000 annual deaths.[1–4] It is also a disease of high and rising incidence and prevalence, estimated at about 400,000 to 700,000 annual new cases with a prevalence approaching 5 million.[5,6] As a consequence, the care of patients with CHF exacts a large and increasing portion of the national health care expenditure, estimated in 1994 to approach $40 billion.[6–8]

On the positive side, several large clinical trials conducted over the past two decades provided evidence for the optimal care of patients with CHF and lead to the formulation of evidence-based practice guidelines. These studies showed that angiotensin-converting enzyme (ACE) inhibitors, used in study doses, have a significant, favorable impact on morbidity and survival.[1,2,9–17] Studies also suggest that higher doses of ACE inhibitors result in better clinical outcomes.[18–20] Yet, the utilization and doses of ACE inhibitors remain lower than the desired targets.[1,6,19–33] Clinical trials have also suggested beneficial roles for beta blockers, angiotensin receptor blockers (ARB), spironolactone, amiodarone, and the hydralazine-nitrates combination.[3,34–44] All of these drugs have been recommended in the most recent practice guidelines for the management of CHF.[45]

Recent data also suggest that care of patients with CHF at specialized comprehensive heart failure programs is associated with improved clinical outcomes, especially lower hospitalization frequency and better survival.[24,46–51] In a randomized study, Rich *et al.* found that a nurse-directed intensive follow-up program resulted in improved hospitalization-free survival in elderly patients discharged from the hospital with

Address for reprints:

Tarik M. Ramahi, M.D.
Section of Cardiovascular Medicine
Yale School of Medicine
135 College Street, Suite 301
New Haven, CT 06510-2483, USA

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CHF.[46] Another recent study showed that specialized heart failure care was associated with an impressive reduction in rehospitalization frequency and significant increase in the average dose of loop diuretics.[24] This study was conducted to evaluate the effect of care in a specialized heart failure program on the utilization and dosage of all cardiovascular drugs that have been shown beneficial in heart failure.

Methods

Study Population

All patients with CHF referred to the Yale Heart Failure and Transplant Cardiology Program between July 1993 and December 1997 were identified. Patients with left ventricular systolic dysfunction (LVEF ≤ 40%) and without endstage renal disease were included in this study. Those with < 2 months of follow-up were excluded. A total of 133 patients (101 men, 32 women, mean age 54 ± 11 years [range 21–83]), met these criteria. Forty-four patients had coronary artery disease and 89 had nonischemic cardiomyopathy. Mean serum blood urea nitrogen was 24 ± 15 mg/dl (range 7–128), and creatinine 1.3 ± 0.4 mg/dl (range 0.7–2.4). Patients' characteristics are described in Table I.

Program Description

Patients underwent individualized baseline evaluation that included assessment of ventricular function, exercise capacity, ambulatory rhythm recording, and, when appropriate, right heart catheterization, myocardial perfusion and viability assessment, coronary angiography, and electrophysiologic evaluation. Patients were reevaluated frequently after initial referral for refinement of medical regimen. Those with severe circulatory insufficiency underwent hemodynamically guided intravenous diuretic, vasodilator, and/or inotropic therapy in a cardiac care unit, followed by institution of maintenance oral medical regimen. Neither intermittent nor chronic intravenous inotropic therapy was utilized. Decisions regarding revascularization, valvular surgery, or transplantation were made on the basis of accepted clinical criteria. Patient care was coordinated by experienced heart failure nurses under the direction of specialized heart failure cardiologists. Education, counseling, and social support were provided by nurses, allied health care staff, and social workers.

Medications

The utilization of cardiovascular medications was evaluated at the time of referral and after at least 1 month of follow-up when patients were deemed in stable circulatory state on optimal medical regimen. The daily doses of ACE inhibitors were normalized to the average doses used in clinical trials such that a normalized dose of 1 was equivalent to 150 mg of captopril, 20 mg of enalapril, 20 mg of lisinopril, 20 mg of quinipril, and 10 mg of ramipril.[1,2,9,11,12,14–17] For the purpose of this study, the ARBs losartan and valsartan were treated similarly to ACE inhibitors; they were used only in patients who were intolerant of ACE inhibitors because of cough. The doses of beta blockers were normalized to a daily carvedilol or metoprolol dose of 100 mg.[34] The doses of nitrates were likewise normalized such that 1 was equivalent to a daily isosorbide dinitrate dose of 160 mg, isosorbide mononitrate dose of 120 mg, and nitropatch of 0.6 mg/h daily.[3]

Hospitalization and Survival

Hospitalization, transplantation, and survival data for all 133 patients were obtained from patient records and computerized database. Heart failure hospitalizations were defined as those for symptoms of congestion or low cardiac output, while

TABLE I Patients' characteristics at initial evaluation and last follow-up visit

Variable	At referral	At follow-up	p Value
Number	133	133	
Age, years	54 ± 11		
Sex, M/F	101/32		
Etiology of heart failure:			
CAD-related cardiomyopathy	44		
Nonischemic cardiomyopathy	89		
Functional class	3.1 ± 0.6	2.7 ± 0.7	< 0.001
LV ejection fraction, %	19 ± 8		
Repeated LVEF, n = 78	19 ± 8	26 ± 11	< 0.001
Systolic BP, mmHg	108 ± 16	107 ± 17	NS
Diastolic BP, mmHg	71 ± 12	67 ± 10	0.003
Blood urea nitrogen, mg/dl, n = 104	24 ± 5	25 ± 15	NS
Serum creatinine, mg/dl, n = 127	1.3 ± 0.4	1.4 ± 0.5	0.02

Abbreviations: M = male, F = female, CAD coronary artery disease, LV = left ventricular, LVEF = left ventricular ejection fraction, BP = blood pressure.

cardiovascular hospitalizations included all other cardiovascular causes. Only nonelective hospitalizations were considered in the analysis. The frequency of nonelective cardiovascular and heart failure hospitalization was determined for the 3-, 6-, and 12-month periods after referral.

Statistical Analysis

Data were expressed as mean ± standard deviation. Continuous variables were compared using Student's *t*-test. Probabilities of hospitalization-free survival were determined using product-limit (Kaplan-Meier) analysis, for which cardiac transplantation and death were treated as censored events. Probability of survival was also determined by the Kaplan-Meier method, and cardiac transplantation was again treated as a censored observation. A p value < 0.05 was considered statistically significant.

Results

Clinical Status

A total of 133 patients met the study criteria. They were followed for a mean duration of 17 ± 14 months (range 1–56 months). (One patient underwent cardiac transplantation 1 month after initial evaluation and was included in the analysis.) Patients' characteristics at follow-up are summarized in Table I. During this period, 20 patients died before transplantation and 22 underwent cardiac transplantation. New York Heart Association (NYHA) functional class was 3.1 ± 0.6 at referral and 2.7 ± 0.7 at last follow-up ($p < 0.001$). Mean left ventricular ejection fraction (LVEF) was 19 ± 8 (range 4–40%). For the 78 patients who underwent reassessment of left ventricular function, LVEF improved from 19 ± 8 to 26 ± 11 ($p < 0.001$).

Drug Utilization

At referral, 87% of the patients were on either ACE inhibitors (86%) or ARB (2%), and at follow-up 95% ($p < 0.04$) were on ACE inhibitors and 100% were on either ACE inhibitors or ARB ($p < 0.001$). Furthermore, the normalized average dose of ACE inhibitors increased by 60% from 0.70 ± 0.52 to 1.11 ± 0.57 ($p < 0.001$), equivalent to daily captopril doses of 105 ± 78 and 167 ± 86 mg, respectively (Table II). No significant change was noted in either utilization or dose of loop diuretics. However, utilization of combination diuretics (loop diuretics plus either metolazone and/or spironolactone) increased significantly from 10 to 23% for metolazone and from 1 to 36% for spironolactone. Significant increases were also noted in the utilization of beta blockers (from 16 to 37%), amiodarone (from 7 to 15%), hydralazine (from 1 to 9%), and nitrates (from 20 to 33%). There was no change in either utilization or dose of digoxin. Only nine patients were on calcium-channel blockers at initial evaluation and six at last follow-up. With this intensification of cardiovascular medical therapy there was no significant change in systolic blood pressure (BP) (108 ± 16 to 107 ± 17), but a slight decrease in diastolic BP from 71 ± 12 to 67 ± 10 ($p = 0.003$). There was no significant change in mean serum BUN, but serum creatinine increased slightly from 1.3 ± 0.4 to 1.4 ± 0.5 ($p = 0.02$).

Survival and Hospitalization

Annualized 1-year survival for the entire group was 90% (Fig. 1). The annualized hospitalization-free survival for the entire group was 66% for cardiovascular hospitalization and 68% for heart failure hospitalization (Fig. 1). Heart failure hospitalization frequencies were 4% at 3 months, 7% at 6 months, and 11% at 12 months. Total cardiovascular hospitalization frequencies were 6% at 3 months, 11% at 6 months, and 22% at 12 months.

TABLE II Utilization and doses of cardiovascular medications at initial evaluation and follow-up

	At referral			At follow-up			
Drug	n[a] (%)	Dose	SD	n[a] (%)	Dose	SD	p Value
ACEI[b]	114 (86)	0.70	0.52	126 (95)	1.11	0.57	<0.001
ARB[b]	2	1.0		9	1.2	0.78	0.06
ACEI or ARB[b]	116 (87)	0.70	0.52	133 (100)	1.11	0.56	<0.001
Digoxin	103	0.22	0.08	115	0.21	0.09	NS
Furosemide	115	94	95	126	103	74	NS
Metolazone	13	3.9	1.3	30	2.9	0.95	0.007
Spironolactone	1	12.5		48	24.2	13.7	<0.001
Hydralazine	1	30		12	194	124	0.004
Nitrates[b]	27	0.44	0.22	44	0.62	0.33	0.03
Beta blockers[b]	21	0.43	0.31	49	0.60	0.41	<0.001
Amiodarone	9	667	548	20	365	173	0.05

[a] Number of patients on the drug.

[b] Dose normalized (see Methods).

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, NS = not significant.

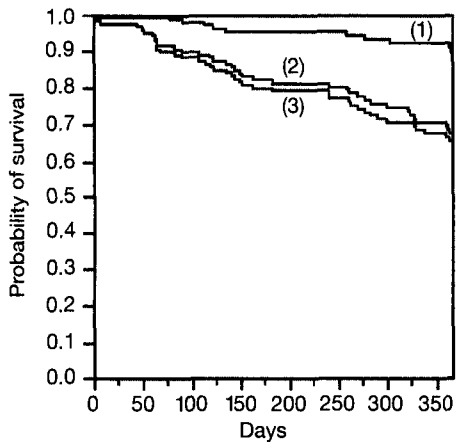

FIG. 1 Kaplan-Meier curves of (1) the probability of survival during the first year after referral, and the probabilities of not being hospitalized for (2) heart failure and for (3) cardiovascular problems during the first year of follow-up.

Discussion

Recently published data provided evidence for the superiority and cost effectiveness of specialized heart failure care.[24, 46, 47, 49–51] This study examined the effect of specialized care on the pharmacologic therapy of patients with heart failure. It showed that care at a specialized heart failure clinic was associated with increase in the utilization of all known beneficial cardiovascular drugs, significant increase in the dose of ACE inhibitors, and intensification of diuretic regimen. Clinically, this was associated with improvement in functional capacity and ventricular function. The increase in the dose of ACE inhibitors and utilization of diuretics was associated with only minor increase in serum creatinine. The heart failure hospitalization rate for this group of patients was low, and the 1-year survival was 90%, both comparable with data reported for similar populations followed at other specialized heart failure programs.[24, 50, 51]

This improvement in cardiovascular pharmacologic therapy may be one of the major reasons accounting for the better clinical outcomes in specialized programs. It involves higher utilization and doses of ACE inhibitors, more intense diuresis, and higher utilization of ARBs, spironolactone, beta blockers, amiodarone, and the combination of hydralazine and nitrates. All of these drugs have been shown or strongly suggested to improve outcomes in CHF.[1–3, 9–12, 14–18, 24, 34–45] There are other reasons for the superior outcomes at specialized programs: they include the comprehensive preventive nature of the care, based on frequent evaluation and close interaction with specialized experienced staff.[46] This often results in the identification of problems at early stages. It also allows for the provision of nonpharmacologic interventions, such as disease- and medication-specific education, dietary counseling, social and psychologic support, and cardiac rehabilitation. Another probable reason is the availability of advanced therapeutic modalities, such as risk stratification and prevention of serious arrhythmia, high-risk revascularization procedures, cardiac transplantation, and a host of medical and surgical experimental treatments.[49]

Several reasons explain the higher utilization and doses of cardiovascular drugs noted in this study. They include more precise and optimal management of diuretics, a proactive preventative approach aiming for maximal neurohormonal inactivation, and the presence of a process designed to deliver this intensive approach. This study and others suggest that patients with CHF are often inadequately diuresed.[24] The consequent suboptimal cardiac loading conditions make it difficult for patients to tolerate the initiation and uptitration of ACE inhibitors and other neurohormonal attenuating agents. This study and others showed that specialized heart failure care was associated with more intense diuresis, either by combination diuretics or higher doses of loop diuretics.[24] Another reason for the underdosing of ACE inhibitors by nonspecialists is the almost exclusive reliance on the "hemodynamic" model for heart failure, aiming to achieve a "compensated" state, rather than the pursuit of a preventative approach based on maximal inactivation of neurohormonal mechanisms. Angiotensin-converting enzyme inhibitors are often considered as vasodilators whose benefits accrue from afterload reduction, rather than neurohormonal inactivation. They are often used to optimize the circulation when the patient is least likely to tolerate them due to low cardiac output. Compounding the problem is excessive concern about advancing the dose of ACE inhibitors in patients with asymptomatic relative hypotension and in those with mild chronic renal insufficiency,[19, 20, 29, 30, 32] despite the proven renal protective effect of ACE inhibitors. Finally, there is the presence in heart failure programs of a process designed to deliver this time- and personnel-intensive approach, allowing for frequent reassessment, the adoption of a comprehensive preventative approach, and the ability to finance such a resource-intensive approach.

This study was a retrospective analysis of data from a single heart failure program involving a relatively young population with systolic heart failure. It nevertheless shows that many patients with CHF were referred by cardiologists for consideration of cardiac transplantation on suboptimal cardiovascular medical regimens. Although the natural course of this disease is progressive deterioration, often associated with decrease in the dose of ACE inhibitors, the study cohort had a significant increase in the dose after an average follow-up of 17 months. Associated with the improvement in pharmacologic therapy were low hospitalization rates and better survival than that expected after cardiac transplantation.[52] The lack of stratified randomized design makes it difficult to compare clinical outcomes based on difference in drug utilization and dose. Although it also makes it impossible to conclude with absolute certainty that the observed improvement in pharmacologic therapy was solely due to specialized care, it is difficult to provide other credible explanations. Considering the study cohort as its own historic control and specialized heart failure care as the intervention that applied to all members, it seems most likely that the observed improvement in pharmacologic therapy was a consequence of specialized care. Although the improve-

ment in the utilization of beta blockers and spironolactone might be a reflection of the recent availability of supportive evidence, this cannot be said for ACE inhibitors, diuretics, and the combination of hydralazine and nitrates.

The improved adherence to practice guidelines demonstrated in this study is likely responsible to a great extent for the beneficial effect of heart failure programs on clinical outcomes. In view of the epidemic nature of heart failure, this finding has important public health implications. It suggests that the proven benefit of cardiovascular medications has yet to be realized by a large portion of the heart failure population. It would be unrealistic, however, for all patients with heart failure to be cared for at regional comprehensive heart failure centers. Patients referred to these centers tend to have advanced disease, and, although they often stand to benefit, the relative benefit would be less than that derived by patients in earlier stages of disease. From a public health perspective it would be more effective to provide optimal preventative care to patients with less advanced stages of disease who are often cared for by primary care providers. Heart failure centers should therefore play a leading role in the continued education of primary providers in the optimal management of heart failure. The quality of this care should perhaps be monitored and assured by the agencies (governmental, HMOs, and insurance companies) that finance this care. These agencies should allow for the adequate reimbursement of the resource-intensive care necessary to achieve the desired cost-effective outcomes. Clearly this is a problem that requires creative concerted effort and oversight.

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