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Factors Determining Angiotensin-Converting Enzyme Inhibitor Underutilization in Heart Failure in a Community Setting

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Summary

Background: Angiotensin-converting enzyme (ACE) inhibitors were underprescribed for patients with congestive heart failure (CHF) treated in the community setting in the early 1990s despite convincing evidence of benefit.

Hypothesis: We postulated that (1) the prevalence of ACE inhibitor use has increased, and (2) prescribing biases have narrowed, as community physicians have gained additional clinical experience with these drugs for treatment of CHF.

Methods: We examined rates of ACE inhibitor use among 1,150 patients with CHF hospitalized at 10 community hospitals in 1995, evaluated determinants of ACE inhibitor prescription, and compared the results with survey data gathered among similar patients during 1992.

Results: Compared with 1992, ACE inhibitor use prior to hospital admission was increased among all patients (42 vs. 33%, $p < 0.001$) and the subset with a history of CHF (53 vs. 39%, $p < 0.0005$). Angiotensin-converting enzyme inhibitor prescription at hospital discharge also increased among all survivors (64 vs. 51%, $p < 0.00005$) and the subset eligible for ACE inhibitor treatment based on clinical trial criteria (77 vs. 66%, $p = 0.04$). Multivariate analysis suggested no change in the prescribing biases previously observed; ACE inhibitor use was related to lower ejection fraction, lower serum creatinine, documentation of left ventricular systolic function, younger patient age, prescription of any diuretic drug, and nonprescription of alternate vasodilators and calcium blockers. In multivariate analyses, physician specialty did not predict ACE inhibitor use.

Conclusions: Angiotensin-converting enzyme inhibitor use among patients with CHF is increasing but remains below the 80–90% rates of drug tolerance documented in randomized clinical trials. This discrepancy is partially explained by the prevalence of renal impairment and "diastolic" heart failure in the community setting. However, age bias, use of alternative vasodilators, and substandard quality of care may also play a role.

Key words: congestive heart failure, angiotensin-converting enzyme inhibitors, diastole

Introduction

Research and clinical experience have defined a role for angiotensin-converting enzyme (ACE) inhibitors in the treatment of congestive heart failure (CHF). These agents improve symptoms[1–5] and quality of life,[6] and improve survival and reduce serious cardiovascular events among patients with symptomatic[3–5,7] and asymptomatic[8] left ventricular contractile dysfunction. The use of ACE inhibitors is a cost-effective strategy[9] and is recommended by expert panels in this country[10] and others.[11] Most patients with CHF tolerate these agents; drug withdrawal due to adverse effects or patient or physician choice occurred in only 10–20%[3,12] of patients in randomized clinical trials.

Despite this information, surveys in the early 1990s demonstrated much lower rates of ACE inhibitor use among patients with CHF treated in the community setting.[12–14] We reported that only 51% of patients received ACE inhibitors following hospitalization for CHF among a sample of 424 individuals treated at two community hospitals during 1992.[14] In this study, the underutilization of ACE inhibitors was related to older patient age, impaired renal function, normal left ventricular systolic function, poor quality medical care, and the use of alternate vasodilators, beta blockers, and calcium blockers.

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Other authors have also suggested that ACE inhibitor prescription practices may vary among medical specialists.[15,16]

We sought to test the following hypotheses: (1) The rate of ACE inhibitor use has increased among patients with advanced CHF treated in the community as a result of continued educational efforts and guidelines; (2) prescribing biases have narrowed, as community physicians have gained additional clinical experience with these drugs for treatment of CHF; and (3) physician specialty training is an important determinant of ACE inhibitor prescription.

Patients and Methods

Patients

The database of the Management to Improve Survival in Congestive Heart Failure (MISCHF) Study was utilized. The design of the MISCHF Study has been reported.[17] In brief, this project involves the collaboration of 10 acute care community hospitals in the study of quality of care for CHF patients. Two of these 10 hospitals were the sites for our 1992 survey. Between April 1 and December 31, 1995, all patients assigned to diagnosis-related group (DRG) 127 (CHF and shock) were enrolled. In addition, patients assigned to DRG 124 (cardiac catheterization with complex diagnosis), whose principal diagnosis was one of the ICD-9-CM codes required for assignment to DRG 127, were also included. By current coding standards, this latter group includes patients whose principal diagnosis was compatible with CHF, but by virtue of having undergone diagnostic cardiac catheterization they were assigned to DRG 124 instead of to DRG 127.[18,19] Patients with a secondary diagnosis of CHF and those undergoing invasive treatment were not enrolled in the MISCHF Study. Patients in the MISCHF Study without a complete chart abstract were excluded from the current analysis. Institutional review boards of all of the participating centers approved the study.

Chart Review

Trained chart reviewers abstracted the medical records of all eligible patients immediately after hospital discharge. For patients hospitalized more than once during the study period, only the first admission was included in this analysis. The presence of CHF was confirmed independently by the chart auditors based on the documentation of typical symptoms, physical findings, laboratory results, and response to appropriate medical therapy. A total of 148 variables was recorded for each patient; they were chosen because of their relevance to clinical issues in CHF.[20–23] Included were demographics, medical and CHF history, and laboratory values and body weight at admission and discharge. Diagnostic and therapeutic modalities, including medication use at admission and discharge, were also recorded. Total comorbid disease was quantified using the Charlson Comorbidity Index.[24]

Data Management and Statistical Analyses

Raw data obtained by chart review were double-entered by experienced clerks on personal computers at a core laboratory experienced in epidemiologic and survey research, using commercially available software (Q&A, Symantec Corporation, Cupertino, Calif.). Data were later transferred to a VAX-3190 computer using SAS software (SAS Institute, Cary, N.C.) for statistical analyses.

Chi-square tables were used to compare the rates of ACE inhibitor prescription in the 1995 cohort with those reported in the previous survey. Chi-square tables (for categorical variables) and Student's *t*-test (for continuous variables) were used to test for clinical and laboratory differences between the 1995 and 1992 samples. As in our previous survey, chi-square tables and Student's *t*-test were used to test for clinical, laboratory, and concomitant treatment differences between patients prescribed and not prescribed ACE inhibitors among the 1995 cohort. After performing univariate tests, stepwise multiple logistic regression was used to determine those factors which had the strongest relationship with ACE inhibitor prescription at discharge. A p value of ≤ 0.10 was used for inclusion of variables into the model and for removal of variables. In interpreting results, a p value of ≤ 0.05 was considered statistically significant. Data are presented as mean ± standard deviation.

Results

Patients

In all, 1,402 patients were enrolled in the MISCHF Study at the 10 participating centers during the 1995 study period. Of these, 252 did not have a complete chart abstract performed and were excluded from this analysis. Sixty-three patients included in this analysis died in the hospital; their data were censored from the analyses of predictors of ACE inhibitor prescription at hospital discharge. Table I reveals the demographic and laboratory characteristics of the 1995 study group, stratified by ACE inhibitor prescription or nonprescription at discharge. The majority of patients had severe or moderately severe CHF, with 88% in New York Heart Association functional class III or IV at the time of hospital admission. The principal discharge ICD-9-CM diagnosis code listed on the discharge abstract was "Congestive Heart Failure" (428, 428.0, or 428.1) in 90% of cases. Only one patient was noted to have a principal discharge ICD-9-CM diagnosis code compatible with cardiogenic shock (785.51). In the opinion of the chart auditors, CHF was a principal reason for hospitalization in 96% of cases. Chronic ischemic heart disease/previous myocardial infarction was the most common primary etiology of CHF (44%). Valvular disease (15%), hypertensive heart disease (14%), and acute ischemic disease (9%) were noted less frequently as the primary cause. Absolute contraindications to ACE inhibitor use such as angioneurotic edema were noted in no cases.

The 1995 cohort was similar to the 1992 sample in terms of mean age, race and gender distribution, frequency of Medicaid

TABLE I Clinical and demographic features of patients prescribed and not prescribed ACE inhibitors following hospitalization for CHF during 1995[a]

	ACEI (n = 689)	No ACEI (n = 398)
Male	46	39[b]
Age (years)	74.1 ± 11.6	75.6 ± 12.1[b]
Caucasian (%)	91	95
Medicaid insurance (%)	5	8
Discharged to nursing home (%)	11	15[b]
Charlson Comorbidity Index (%)	2.7 ± 1.6	3.0 ± 1.8[b]
History of CHF (%)	64	60
NYHA functional class at admission	3.4 ± 0.9	3.3 ± 0.9
Baseline body weight, kg	76.8 ± 20.8	74.4 ± 23.2
Atrial fibrillation (%)	28	26
Repetitive ventricular arrhythmia (%)	25	24
Radiographic cardiomegaly (%)	82	78[b]
Left ventricular ejection fraction	0.34 ± 0.15	0.42 ± 0.15[b]
Qualitatively abnormal LV function (%)	65	37[b]
Left atrial size, mm	46 ± 9	44 ± 8[b]
Serum sodium, mmol/dl	138.8 ± 4.5	139.3 ± 4.4
Serum potassium, mEq/dl	4.2 ± 0.6	4.3 ± 0.7
Serum creatinine, mg/dl	1.4 ± 1.0	2.0 ± 2.0[b]

[a] Categorical values are displayed as percentage of the group; continuous variables are displayed as mean ± standard deviation.
[b] $p \leq 0.05$ for comparison between patients prescribed and not prescribed ACE inhibitors.
Abbreviations: ACE = angiotensin-converting enzyme, CHF = congestive heart failure, ACEI = ACE inhibitor, NYHA = New York Heart Association, LV = left ventricular.

insurance, proportion of nursing home residents, history of CHF, mean functional class, and prevalence of sinus rhythm and radiographic cardiomegaly (all $p > 0.05$). In comparing hospital survivors, 1995 patients had a higher mean serum sodium (139 ± 4 vs. 137 ± 8), lower serum creatinine (1.6 ± 1.4 vs. 2.0 ± 0.2), and lower left ventricular ejection fraction (0.37 ± 0.15 vs. 0.42 ± 0.15) (all $p \leq 0.05$).

Prevalence of Angiotensin-Converting Enzyme Inhibitor Use

Table II shows the prevalence of ACE inhibitor use immediately prior to hospital admission for all patients, as well as for the subset with a history of medical care for CHF. Table II also reveals the rate of ACE inhibitor prescription at discharge among hospital survivors. For each group of patients, comparison is made with our observations among similar groups from our 1992 survey. As shown, ACE inhibitor use was increased in all three patient groups.

When analyses were restricted to the 310 patients treated at the two hospitals which also participated in the 1992 survey, similar trends in ACE inhibitor use were observed. Among all patients, 37% were on ACE inhibitors immediately prior to admission ($p = 0.25$ compared with 1992). Among the subset with a history of CHF, 46% were taking ACE inhibitors immediately prior to hospitalization ($p = 0.13$ compared with 1992). Among hospital survivors, 57% were prescribed ACE inhibitors at hospital discharge ($p = 0.16$ compared with 1992).

TABLE II Prevalence of ACE inhibitor use among patients hospitalized for CHF compared with reference year 1992[a]

	1995		1992		
	No. of patients	%	No. of patients	%	p Value[b]
Prior to admission, all patients	1,150	42	424	33	0.001
Prior to admission, only patients with a history of CHF	717	53	288	39	0.0005
Discharge prescription (survivors)	1,087	64	388	51	0.00005

[a] See Reference No. 14.
[b] p Value for comparison of drug prescription rates between 1992 and 1995 patients.
Abbreviations as in Table I.

We screened the two data sets to determine the rates of ACE inhibitor use among those eligible by clinical trial criteria. Eligibility was defined as (1) serum creatinine measured at least twice and all values ≤ 2.5 mg/dl, (2) serum potassium measured at least twice and all values ≤ 5.5 mEq/dl, (3) left ventricular ejection fraction measured within 6 months and ≤ 0.45, and (4) no documented absolute contraindications to ACE inhibitor use. Among such patients, drug use increased from 1992 to 1995 (77 vs. 66%, $p = 0.04$).

Determinants of Angiotensin-Converting Enzyme Inhibitor Prescription

As shown in Table I, substantial differences were observed between patients prescribed and not prescribed ACE inhibitors during 1995. These agents were used more frequently among younger, male patients and those with fewer comorbidities. Patients receiving ACE inhibitors were also less likely to be nursing home residents and have renal impairment, and more likely to have radiographic cardiomegaly, a low left ventricular ejection fraction, and a large left atrium.

Table III reveals the concomitant drug therapy and processes of care among patients prescribed and not prescribed ACE inhibitors. As shown, patients treated with these drugs were less likely to receive alternative (non-ACE inhibitor) vasodilators and calcium blockers, but were more likely to receive digoxin, diuretics, nitrates, and warfarin. Furthermore, patients prescribed ACE inhibitors were more likely to receive care from a cardiologist, undergo diagnostic studies to deter-

TABLE III Concomitant drug therapy and processes of care of patients prescribed and not prescribed ACE inhibitors following hospitalization for CHF during 1995[a]

	ACEI (n = 689)	No ACEI (n = 398)
Other discharge medications		
Alternate (non-ACE inhibitor) vasodilator	4	8[b]
Digoxin	62	46[b]
At least one diuretic drug	88	73[b]
Two diuretic drugs in different classes	7	8
Potassium supplements	39	43
Nitrates	45	38[b]
Beta blockers	12	16
Calcium-channel blockers	22	37[b]
Warfarin anticoagulation	27	17[b]
Processes of care		
Noncardiologist providing care	34	42[b]
CHF etiology documented	77	76
Left ventricular systolic function documented	78	69[b]
Any diagnostic study for CHF etiology	73	64[b]
Echocardiogram or nuclear ventriculogram	57	47[b]
Exercise stress test	10	8
Cardiac catheterization	12	14

[a] Categorical values are displayed as percentage of the group.
[b] $p \leq 0.05$ for comparison between patients prescribed and not prescribed ACE inhibitors.
Abbreviations as in Table I.

TABLE IV Results of multivariate analysis: Strongest predictors of ACE inhibitor prescription following hospitalization for CHF during 1995

Predictor	Odds ratio	Confidence intervals	p Value
Lower left ventricular ejection fraction	0.9660	0.9530–0.9792	0.000001
Taking any diuretic drug	3.1709	0.9464–5.1660	0.000004
Lower serum creatinine	0.7562	0.6293–0.9806	0.003
Left ventricular systolic function documented	4.1863	1.3686–12.8051	0.012
Younger patient age	0.9764	0.9586–0.9946	0.011
Taking alternate vasodilator	0.3923	0.1831–0.8407	0.016
Taking calcium-channel blocker	0.6166	0.4000–0.9504	0.028

Abbreviations as in Table I.

mine the etiology of CHF, have their left ventricular systolic function documented in their hospital chart, and undergo echocardiography or nuclear ventriculography.

The results of the multivariate analyses are shown in Table IV. Factors with the strongest relationship with ACE inhibitor prescription were lower ejection fraction, lower serum creatinine, documentation of left ventricular systolic function, younger patient age, prescription of any diuretic drug, and nonprescription of alternate vasodilators and calcium-channel blockers. None of the other factors which achieved statistical significance at the univariate level, including physician specialty, remained in the final multivariate model for ACE inhibitor use.

Discussion

The principal findings of this study are as follows: (1) The prescription of ACE inhibitors among patients with CHF treated in the community setting is increasing; (2) among eligible patients, the use of ACE inhibitors is approaching the rates observed in randomized clinical trials; (3) among unselected patients in the community, the prevalence of renal insufficiency and "diastolic" heart failure accounts for much of the discrepancy with clinical trial experience; (4) residual underutilization of these drugs may be related to age bias, use of alternative vasodilators and calcium-channel blockers, and poor quality care; and (5) after accounting for case-mix, physician specialty is not an independent predictor of ACE inhibitor use.

The relevance of these practice patterns warrants comment. Two factors which appear to direct physicians away from the use of ACE inhibitors—preserved left ventricular systolic function and renal impairment—may reflect on limitations of the current body of knowledge regarding the role of these drugs in CHF. Preserved or normal left ventricular systolic function is present in up to 40 to 45% of patients with symptomatic CHF.[25–27] There is little published evidence to guide clinicians in the use of ACE inhibitors when CHF is attributed to "diastolic" heart failure.[26] A case-control series demonstrating ACE inhibitor efficacy among patients with CHF and ejection fractions ≥ 0.40 has been published.[27] However, there are no large-scale studies that test this hypothesis in a prospective, randomized fashion. In fact, admonitions against the use of potent vasodilators in CHF when the ejection fraction is normal[25] could be interpreted as advice against the use of ACE inhibitors. Until the benefits of ACE inhibition in "diastolic" heart failure are known, such patients will account for a sizable portion of those with CHF who do not receive ACE inhibitors in the community setting. Similar comments might be made about the use of ACE inhibitors among patients with renal impairment. Because these drugs may worsen kidney function, particularly among those with preexisting renal disease,[28] patients with elevated serum creatinine values were excluded from the large ACE inhibitor mortality trials.[5,8] Thus, there is limited information on the impact of ACE inhibition on outcomes in CHF among patients with creatinine values ≥ 2.0–2.5 mg/dl,[29] despite the negative prognosis associated with renal dysfunction in CHF. It is likely that ACE inhibitor use among

those with renal dysfunction will remain low until there is good evidence of their benefit.

The results of VHeFT-I[30] suggest that the combination of hydralazine and isosorbide is an effective vasodilator strategy in CHF. However, the results of VHeFT-II[7] have led many experts to conclude that this combination should be reserved for those intolerant to ACE inhibition. Moreover, the substitution of calcium blockers for ACE inhibitors in CHF is a practice that is difficult to defend.[31] In the current study, 37% of patients off ACE inhibitors were prescribed calcium blockers. Although calcium blockers may have been prescribed for "diastolic failure"[25] in some cases, multivariate analysis revealed that calcium blocker use remained predictive of ACE inhibitor nonprescription even after adjustment for ejection fraction and other variables. Thus, some clinicians may view calcium blockers as vasodilators appropriate for use in CHF.

Our results support the hypothesis that ACE inhibitor use reflects overall quality of care. In addition to the calcium blocker phenomenon, we observed an age-related prescription bias which cannot be defended by the existing literature. Although patient age may be a proxy for some other unmeasured variable in our population, the findings are consistent with bias against invasive or appropriate treatment of older patients with other forms of cardiovascular disease.[32] Finally, failure to document systolic function during treatment for CHF correlated with failure to prescribe ACE inhibitors, again suggesting that drug use reflects quality and appropriateness of care.

After adjusting for case-mix, we observed no effect of physician specialty on drug prescription rates, in contrast to previous reports.[15, 16] Unlike Stafford and colleagues[15] we adjusted prescription rates for patient-specific characteristics which are associated with drug use. Unlike Shah *et al.*,[16] we measured physician practice, not self-reported behavior. We conclude that the raw rate of ACE inhibitor use among groups of individuals cannot be interpreted as a process indicator of quality without accounting for differences in patient case-mix.

We observed only a modest increase in ACE inhibitor use between the years 1992 and 1995, despite large scale clinical trials demonstrating the efficacy of ACE inhibitors in CHF,[1–8] and guidelines for CHF management advising ACE inhibitor use from both government agencies and medical organizations.[10, 11, 33] In general, the medical community has become more conscious of the need to examine cost effectiveness and quality in health care.[34] Our observations suggest that landmark medical events and driving socioeconomic forces have had an only modest impact on physician practice.[17] Whether more rigorous disease management strategies[35] will facilitate higher quality medical care on a more widespread basis is unknown.

Study Limitations

Without specific data on physicians' attitudes toward treatment of CHF, we cannot directly prove our hypotheses regarding bias in drug choice and practice patterns. Our analysis was limited to the care of patients at 10 hospitals. Whether the conclusions apply to other geographic regions and other institutions is not known. Because tertiary services for CHF were unavailable at all of the centers in this study, we cannot report on the prevalence of drug prescription among heart failure specialists.[16] We focused on inpatient management; our observation of outpatient practice was limited to the rate of ACE inhibitor prescription prior to hospitalization among patients who had a history of CHF. We are unable to provide information about the adequacy of ACE inhibitor dosing among those who received these drugs.

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