Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Patients with Congestive Heart Failure: An Observational Study of Treatment Rates and Clinical Outcome

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Abstract

Background: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers improve prognosis in congestive heart failure and are the treatment of choice in these patients. Despite this, the rates of ACE-I usage in heart failure patients remain low in clinical practice.

Objectives: To evaluate the rate of ACE-I/ARB treatment in hospitalized patients with CHF, and analyze the reasons for non-treatment.

Methods: We prospectively evaluated 362 consecutive patients hospitalized with CHF. Patients were evaluated for ACE-I/ARB usage at discharge and were followed for 1 year.

Results: At hospital discharge 70% of the patients were prescribed ACE-I/ARB treatment. Only 69% received recommended target or sub-target dosages, proven to improve prognosis. This decreased to 63% and 59% at 6 months and 12 months of follow-up respectively, due to a shift from sub-target levels to low dosages. Justified reasons for under-treatment were apparent in only 25% not optimally treated discharged patients and this decreased to 12% and 4% at 6 and 12 months follow-up, respectively. Common reasons for non-treatment at discharge were hyperkalemia and elevation in serum creatinine, while hypotension and cough were more prominent at follow-up. Clinical parameters associated with increased treatment rates were ischemic heart disease and the absence of chronic renal failure. Patients receiving treatment had lower hospitalization and mortality rates.

Conclusions: ACE-I/ARB treatment is still underutilized in patients discharged from hospital with a diagnosis of CHF. Increasing the awareness of the importance of these drugs may increase the number of patients treated.

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Angiotensin-converting enzyme inhibitors are the first line of drugs in the treatment of congestive heart failure. Angiotensin receptor blockers are first-line drugs if there is intolerance to ACE-I. These classes of drugs have been shown in numerous randomized controlled trials to reduce morbidity and mortality in patients with CHF [1-4]. In addition, the combination of both drugs may have clinical benefit in appropriate patients [5]. ACE-I treatment has significantly reduced the rehospitalization rate in these patients [6,7] and is cost effective [8].

ACE-I = angiotensin-converting enzyme inhibitors
ARB = angiotensin receptor blockers
CHF = congestive heart failure

Despite the undisputed benefit of ACE-I treatment, studies suggest that the rate of ACE-I usage in heart failure patients remains low in terms of the number of patients treated and ACE-I target doses. Low (insufficient) dosages are entrenched in current practices despite clear guidelines regarding the usage and optimal dosage of ACE-I in CHF [9-11]. This has been shown to increase the morbidity and mortality rate in patients without or with insufficient ACE-I treatment as compared to patients with recommended doses of ACE-I [6-11]. Few data exist concerning the reasons for this anomaly. It could be due to side effects, the treating physician's unawareness, or reluctance due to perceived side effects, like renal failure or hyperkalemia, or to patient non-compliance.

Since regular and adequate treatment with ACE-I reduces hospitalizations for heart failure and also mortality, the objectives of this study were to investigate treatment rates of ACE-I/ARB in patients hospitalized with CHF and analyze the reasons for non-treatment. In addition, we examined clinical parameters that influenced ACE-I/ARB usage and the clinical outcome in these patients.

Patients and Methods

We prospectively enrolled consecutive patients with CHF admitted to an internal medicine department with a definite diagnosis of CHF not necessarily related to the hospital admission. Diagnosis of heart failure was based either on clinical symptoms and signs consistent with heart failure or reduced left ventricular function. Clinical diagnosis of CHF was based on multiple symptoms and signs consistent with heart failure: orthopnea, paroxysmal nocturnal dyspnea, elevated jugular pulse, leg edema and enlarged heart silhouette on chest X-ray. The echocardiographic inclusion criterion was reduced left ventricular function. Classification of left ventricular function was qualitative using a visual assessment of mild, moderate or severely reduced left ventricular function. The study protocol was approved by the Hadassah-Hebrew University Medical Center Institutional Committee for Human Studies.

Hospitalization evaluation

Data on sociodemographic status including place of residence, ethnic background, education, background (concurrent) diseases as documented by the medical records, the causes of admission

and drug prescription on discharge, were recorded systematically on to predefined data extraction sheets by a clinical pharmacologist from the medical records during hospitalization. Dosages of ACE-I or ARB on discharge were noted. Reasons for non-prescription, withdrawal or replacement of the drug were evaluated, as were side effects. These data were extracted from the patients' files.

Follow-up evaluation

Patients and their family physician were followed by telephone interview with a clinical pharmacologist for a period of 1 year after discharge. This was conducted at 6 and 12 months after discharge. The data collected included the usage and dosage of ACE-I and ARB and the reasons for a change in prescription. Clinical outcomes were also evaluated, including hospital readmission, its reason, and death. Mortality was based on data from the National Census Bureau.

Definition of optimal ACE-I dosage

Doses of ACE-I were classified as target, sub-target, or low, according to the dosing strategies used in randomized clinical trials and the recommendations of clinical guidelines. Target doses were classified as doses higher or equal to those recommended in the practice guidelines that were shown to improve survival in the clinical trials. Sub-target doses were classified as doses that, although lower than guideline recommendations, still demonstrated mortality benefit in the clinical trials. Low doses were classified as doses lower than the minimum dosing used in the clinical trials. The sub-target and target dosages of the drugs (in mg) were: captopril 6.25–12.5 tid, 25–50 bid, tid; enalapril 2.5–5 bid,10 bid; ramipril 1.25–5 qd, 5 bid; cilazapril 0.5 qd, 1–2.5 qd; lisinopril 2.5–5 qd, 10–20 qd; fosinopril 5–10 qd, 20 qd; benazapril 5 qd, 10 qd; losartan 25–50 qd, 50–100 qd; candasartan 8–16 qd, 32 qd; irbesartan 75–150 qd, 150 qd; and valsartan 80–160 bid, 160–320 bid.

Statistical analyses

Analysis was done by SPSS commercially available software. Chi-square analysis was used to examine the bivariate comparisons for each of the demographic or clinical parameters that may affect prescription rate and was assessed in a systematic fashion. Binary logistic analysis was used for multivariate analysis of parameters that affected prescription rate. Analysis of clinical outcome was based on the average dosage of ACE-I/ARB treatment during the period of follow-up. Kaplan-Meier curves, with the log-rank test, were used to compare survival among the groups. Multivariate Cox regression analysis was used to evaluate independent variables that determined survival. A P value of < 0.05 was considered statistically significant.

Results

Clinical parameters

We recruited 362 consecutive patients who were hospitalized with a definite diagnosis of congestive heart failure during the period January 2001 to December 2002. The demographics and

Table 1. Demographics and clinical characteristics of patients with CHF

Age (yrs)	74 ± 12
Range	27–100
Male/Female	194/168
Nursing home	60 (16%)
Admission due to CHF	207 (57.2%)
Concurrent illnesses	
Ischemic heart disease	247 (68.2%)
S/P myocardial infarction	102 (28.1%)
Hypertension	198 (54.7%)
Diabetes mellitus	149 (41.2%)
Chronic renal failure	124 (34.3%)
Hyperlipidemia	99 (27.3%)
Atrial fibrillation	126 (34%)
Chronic obstructive lung disease	96 (26.4%)
Laboratory data on discharge	
Serum creatinine (mean)	162 ± 138 µmol/L (51–1381)
Serum Na+ (mean)	138 ± 6.1 mEq/L (130–151)
Serum Na+ ≤ 135 mEq/L (patients, %)	89 (25%)
Treatment on discharge	
ACE-I	211 (58.3%)
ARB	56 (15.5%)
Beta-blockers	161 (44.5%)
Spironolactone	95 (26.2%)
Furosemide	245 (67.7%)
Digoxin	78 (21.5%)
Nitrates	148 (40.9%)
Calcium channel blockers	81 (22.4%)
Statins	99 (27.3%)
Anticoagulants	78 (21.5%)
Aspirin	187 (51.7%)
Anti-arrhythmic	73 (20.2%)

clinical parameters are presented in Table 1. The primary reason for the hospitalization was heart failure in 57% of the patients. New York Heart Association functional capacity was available in 67% of the patients and the majority of them were in class II and III (34% and 38% respectively). Echocardiographic data were available in 80% of patients. Of these, 35% suffered from clinical heart failure with preserved (normal/good) systolic LVF, 21% from mildly reduced LVF, 13% had moderate LVF and 30% had moderate to severe LVF. Only 1% had severe LVF.

ACE-I/ARB treatment

On hospital discharge, 58.3% (211/362 patients) were treated with ACE-I and 15.5% (56/362) with an ARB. Three percent (11/362) were receiving both drugs. Overall, 70.7% (256/362) received ACE-I/ARB treatment but only 69.3% (251/362) received target or sub-target dosages [Figure 1A]. Only a small percentage (1.4%) received a low dosage treatment. However, target and sub-target rates fell to 63.4% (220/347) at 6 months of follow-up, with 10.4% receiving a low dosage. This rate fell even more at 12 months follow-up to 59.4% (161/271) of the patients. Analysis of each dosage subgroup [Figure 1B] revealed that although there was an
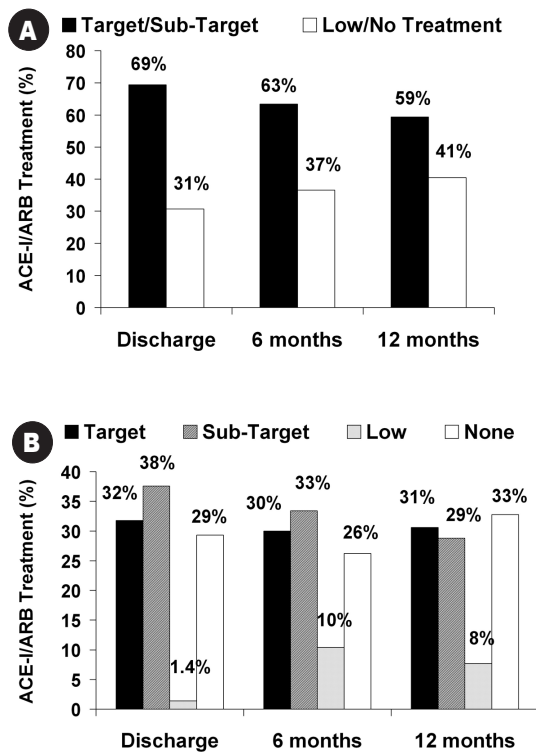
LVF = left ventricular function

Figure 1. ACE-I/ARB treatment in CHF patients discharged from hospital and follow-up of 1 year. Analysis of effective treatment, i.e., target and sub-target dosage versus low and no treatment **[A]**, and analysis of each dosage subgroup separately **[B]**.

and valsartan (1 patient each). Ramipril was the most frequently prescribed drug (46% of the ACE-I/ARB treatment at discharge and this percent was almost unchanged at follow-up). However, only 20% of the patients treated with ramipril received a target dose, while the majority received a sub-target dose (77% of these patients). At follow-up the number of patients who received a target dose decreased to 16% and 19% at 6 and 12 months respectively. The second most frequent prescribed drug was losartan (21%) and the third most frequent drug was enalapril (16%). However, the majority of patients treated with these drugs were prescribed target dosages (losartan 77%, enalapril 57%) and this was constant during follow-up.

An obvious reason for non-treatment (including sub-target, low dose and no treatment) was apparent in only 25% of the discharged patients who were not receiving optimal treatment and this decreased to 12% and 4% at 6 and 12 months follow-up, respectively [Table 2]. Analyzing separately the patients who did not receive target or sub target dosages – 111 patients – only 32 (29%) had a justified reason for this on discharge. Overall, on discharge 22% of the total population (79/362) was not on target or sub-target treatment and did not have a justified reason. The reasons for non-treatment with ACE-I/ARB at hospital discharge were hyperkalemia (63%), elevation in creatinine (54%), hypotension (8%) and cough (2%). At 6 months follow-up the reasons were hypotension (39%), hyperkalemia (26%) and cough (23%).

In order to assess possible factors affecting treatment we analyzed demographic and clinical parameters. This included age, gender, ethnic background, education, resident status (independent versus nursing home), disease severity and concurrent illnesses. We compared patients in target and sub-target treatment groups versus low and no treatment so that the sample size was large enough to have statistical meaning. None of the sociodemographic parameters analyzed demonstrated differences in the rate of prescription (data not shown) with the exception of age and resident status. Patients who received optimal treatment were younger (mean age 73 versus 76 years in patients receiving low or no treatment, $P = 0.08$). Patients living in a nursing home

overall reduction over time in treatment dosages, this was due to a shift from sub-target levels to low dosages, while percent treatment of target dose and no treatment was stable at 30% each at hospital discharge and during follow-up.

ACE-I/ARB drugs prescribed in this study are presented in Table 2. In addition to the drugs mentioned in the table, other prescribed drugs included fosinopril (2 patients), candesartan

Table 2. Drugs prescribed in this study, the percent treated with target dose, and justified rates of non-treatment with ACE-I/ARB

	Hospital discharge		6 months		12 months	
	Patients treated (percent of total drugs)	Target dose	Patients treated (percent of total drugs)	Target dose	Patients treated (percent of total drugs)	Target dose
Ramipril	123 (46%)	25 (20%)	119 (45%)	19 (16%)	86 (47%)	16 (19%)
Losartan	56 (21%)	43 (77%)	59 (22%)	43 (73%)	42 (23%)	35 (83%)
Enalapril	42 (16%)	24 (57%)	40 (15%)	24 (60%)	26 (14%)	17 (65%)
Captopril	31 (12%)	14 (45%)	27 (10%)	8 (30%)	14 (8%)	3 (21%)
Cilazapril	13 (5%)	13 (92%)	13 (5%)	11 (85%)	12 (7%)	10 (83%)
	Hospital discharge		6 months		12 months	
	Not optimally treated	Justified reason	Not optimally treated	Justified reason	Not optimally treated	Justified reason
No treatment	106	29 (27%)	106	2 (1.9%)	180	1 (0.6%)
Low dose	5	3 (60%)	36	15 (42%)	21	4 (19%)
No treatment and low dose	111	32 (29%)	142	17 (12%)	201	5 (2%)
Sub-target	136	29 (21%)	116	14 (12%)	78	5 (6%)
All not optimally treated	247	61 (25%)	258	31 (12%)	279	10 (4%)

were less likely to be optimally treated compared to patients living independently (57% vs. 72%, *P* < 0.05). There was no difference in rate of prescription in relation to the functional capacity or LV function. Patients admitted primarily due to CHF exacerbation were more likely to be prescribed optimal ACE-I/ARB treatment on discharge (73% vs. 64%, *P* = 0.08). The clinical factors that affected prescription rates on discharge were the concurrent illnesses: chronic renal failure, ischemic heart disease, hypertension and diabetes. Patients with chronic renal failure were less likely to be treated with an ACE-I/ARB (63% vs. 72%, *P* < 0.05). Patients with hypertension were more likely to be treated with an ACE-I/ARB (74% vs. 64%, *P* < 0.05). A similar trend was seen with ischemic heart disease (72% vs. 63%, *P* = 0.09) and diabetes (74% vs. 65%, *P* = 0.08). Binary logistic analysis that included the above parameters demonstrated that ischemic heart disease and chronic renal failure were significant independent predictors of ACE-I/ARB prescription rate [Figure 2A].

Clinical outcome

At 6 months follow-up total rehospitalization occurred in 51% of the patients. ACE-I/ARB treatment had an effect on the percent of patients rehospitalized (low/no treatment versus sub-target/target – 59% vs. 47% respectively, *P* = 0.02). ACE-I/ARB treatment also had an effect on the mean hospitalization rate per patient (low/no treatment versus sub-target/target – 1.1 vs. 0.82 respectively, *P*

= 0.04). Total rehospitalization at 12 months occurred in 69% of the patients with a mean hospitalization rate per patient of 1.7. There was no significant difference in 12 month hospitalization between the groups (69% vs. 69%, *P* = 0.5) or mean hospitalization rate per patient (1.82 vs. 1.69, *P* = 0.5). However, analyzing hospitalization primarily due to CHF at 12 months, there was a trend for increased rehospitalizations in patients not optimally treated (low/no treatment vs. sub-target/target 33% vs. 24%, *P* = 0.05) as well as a trend for an increased mean hospitalization rate per patient (1.1 vs. 0.8, *P* = 0.08).

ACE-I/ARB treatment also was related to mortality. Overall survival at 6 months was 86%. There was reduced survival in patients with no or low ACE-I/ARB treatment compared to sub-target/target treatment but this was not significant (82% versus 88% respectively, *P* = 0.13). At 12 months, overall survival was 73%. The survival curve for the 12 month follow-up demonstrated a significant decrease in survival in the group that received no or low ACE-I/ARB treatment compared to the group that received sub-target or target treatment (67% versus 77% respectively, *P* = 0.03). Multivariate Cox regression analysis of the predictors of survival demonstrated that age, male gender, CRF, residence in a nursing home, a discharge sodium ≤ 135 mEq/L were predictors of reduced survival, while beta-blocker and aspirin treatment on discharge were predictors of increased survival [Figure 2B]. ACE-I/ARB treatment was not an independent predictor of increased survival in this analysis.

Discussion

In this study we examined the treatment rates of ACE-I/ARB in patients discharged from a tertiary hospital and during a follow-up of 1 year. We found that the overall treatment rate was 69% at discharge (target and sub-target dosage) and this fell to 63% at 6 months and to 59% at 12 months. The main reason for this decrease over time was a shift from sub-target to a low dose. This finding is consistent with the rate of under-utilization of these drugs in other published studies. Studies evaluating ACE-I treatment in CHF patients discharged from hospital revealed a 55–62% adherence rate [10,12]. In the recent EuroHeart Failure Survey [10] that also included Israel, the overall prescription rate of ACE-I was 62% although the rate of prescription in patients with reduced LVF was almost 80%. There were large variations in the prescription rate between different countries, ranging from 40% to 80%. The reported rate of prescription in Israel was 60%, close to the average
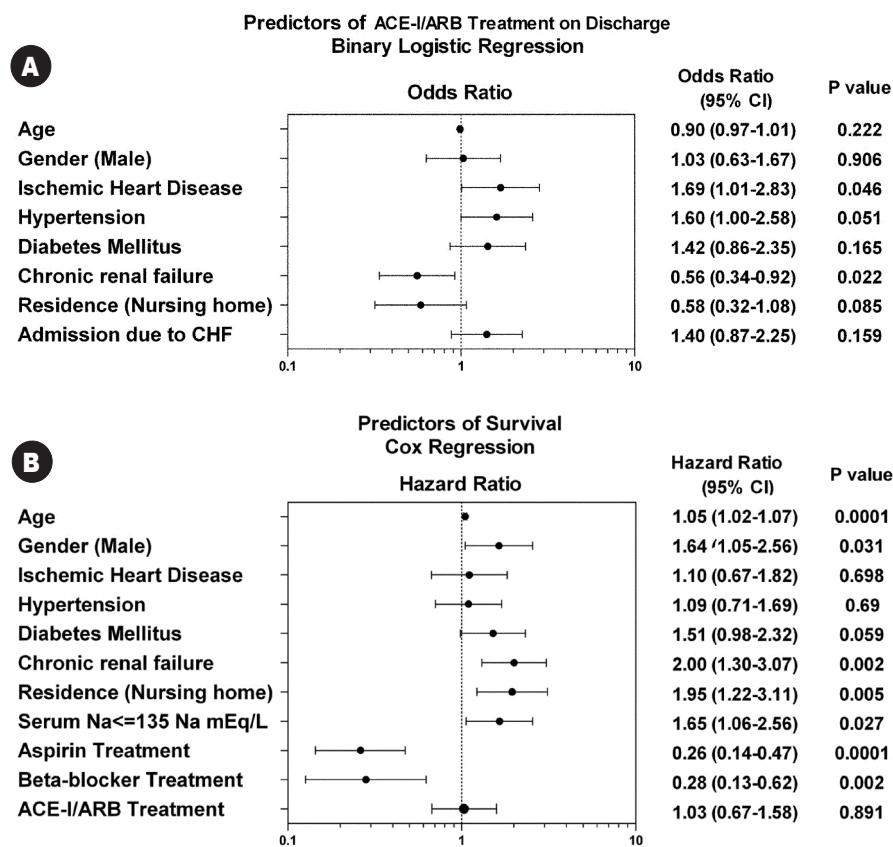
Predictors of ACE-I/ARB Treatment on Discharge Binary Logistic Regression

(A)

	Odds Ratio (95% CI)	P value
Age	0.90 (0.97-1.01)	0.222
Gender (Male)	1.03 (0.63-1.67)	0.906
Ischemic Heart Disease	1.69 (1.01-2.83)	0.046
Hypertension	1.60 (1.00-2.58)	0.051
Diabetes Mellitus	1.42 (0.86-2.35)	0.165
Chronic renal failure	0.56 (0.34-0.92)	0.022
Residence (Nursing home)	0.58 (0.32-1.08)	0.085
Admission due to CHF	1.40 (0.87-2.25)	0.159

Predictors of Survival Cox Regression

(B)

	Hazard Ratio (95% CI)	P value
Age	1.05 (1.02-1.07)	0.0001
Gender (Male)	1.64 (1.05-2.56)	0.031
Ischemic Heart Disease	1.10 (0.67-1.82)	0.698
Hypertension	1.09 (0.71-1.69)	0.69
Diabetes Mellitus	1.51 (0.98-2.32)	0.059
Chronic renal failure	2.00 (1.30-3.07)	0.002
Residence (Nursing home)	1.95 (1.22-3.11)	0.005
Serum Na<=135 Na mEq/L	1.65 (1.06-2.56)	0.027
Aspirin Treatment	0.26 (0.14-0.47)	0.0001
Beta-blocker Treatment	0.28 (0.13-0.62)	0.002
ACE-I/ARB Treatment	1.03 (0.67-1.58)	0.891

Figure 2. Factors independently associated with ACE-I/ARB optimal treatment at discharge by binary logistic regression analysis **[A]**. Predictors of death by Cox regression analysis **[B]**.

European prescription rate. The recent Israeli nationwide heart failure survey (HFSIS 2003) also found low treatment rates in hospitalized CHF patients; only 59% percent of the patients on discharge were treated with ACE-I and 9% were treated with ARB [13,14]. In a recent study, treatment with either ACE-I or ARBs was 86% in low risk patients but only 67% in high risk patients [15]. Thus, these drugs are underutilized in patients with the greatest risk of death.

Of the patients not receiving optimal ACE-I/ARB treatment, only 25% had a justified reason. Even when analyzing only those patients who did not receive target and sub-target dosages, only 29% had an apparent justified reason for not receiving this treatment. This finding is interesting, as it comes from an academic tertiary medical facility. The study design dictated that data be retrieved from the hospital files and not from the treating physician. We did not wish to intervene during the study and bias the data by increasing the treatment rate. It is possible that this caused an underestimation of the reasons for non-treatment. The justified percentage of non-treatment was reduced further during follow-up, with only 4% of the patients with an obvious justified reason at 12 months. As opposed to data on discharge, follow-up evaluation was based on patient interviews and the treating physician. The data are probably an accurate estimation of the justified number of patients under-treated in this cohort. Thus, the data suggest that despite the proven benefits of this treatment modality, at least a fifth of the patients do not receive adequate treatment. More patients with heart failure should be treated.

The clinical factors that had an affect on the treatment rate in our study were age (an inverse relationship), resident status and concurrent illnesses: CRF (inverse relationship), ischemic heart disease, hypertension and diabetes, although not all reached statistical significance on multivariate analysis. The fact that these concurrent diseases (ischemic heart disease, hypertension and diabetes) increased treatment rates is not surprising as these diagnoses are also an indication for ACE-I/ARB treatment and would improve the probability of prescribing these drugs [9].

ACE-I/ARB treatment was associated with a better outcome in our patient cohort, although we did not find an independent effect of ACE-I/ARB treatment on survival in our study. This study was not randomized and not designed primarily for this endpoint; this is not altogether surprising. Nevertheless, ACE-I/ARB treatment has a significant impact on outcome, as evident in multiple large randomized and well-established clinical studies, and treatment with ACE-I/ARB is imperative in patients with CHF.

In conclusion, ACE-I/ARB treatment is still under-utilized in patients discharged with a diagnosis of CHF. Increasing the awareness of the importance of these drugs may increase this treatment for appropriate patients.

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