



Clinical research

Use of angiotensin-converting enzyme inhibitors and variations in cognitive performance among patients with heart failure

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Received 22 June 2004; revised 20 October 2004; accepted 28 October 2004; online publish-ahead-of-print 6 December 2004

KEYWORDS

Heart failure;
Angiotensin-converting
enzyme inhibitors;
Vascular dementia;
Epidemiology

Aims Cognitive dysfunction is a prevalent condition among patients with heart failure, and is independently associated with disability and mortality. Angiotensin-converting enzyme (ACE)-inhibitors might increase cerebral blood flow in subjects with heart failure. Our aim was to assess whether starting treatment with ACE-inhibitors might improve cognition in patients with heart failure.

Methods and results Analyses involved 12 081 subjects, 1220 of whom had a verified diagnosis of heart failure, enrolled in a multi-centre pharmaco-epidemiology survey. None of these participants received ACE-inhibitors before hospitalization. Among participants with heart failure, cognitive performance improved in 30% of 446 participants who started ACE-inhibitors, but only in 22% of remaining patients ($P = 0.001$). Among participants without heart failure, cognition improved in 19% of those receiving ACE-inhibitors, and in 18% of untreated patients ($P = 0.765$). Use of ACE-inhibitors among patients with heart failure was associated with improving cognition (odds ratio = 1.57; 95% CI 1.18–2.08) also in the multivariable regression modelling, independently of baseline or discharge blood pressure levels. The probability of improving cognitive performance was higher for dosages above the median values, as compared with lower doses (odds ratios = 1.90 and 1.42; P for trend = 0.001), and increased with duration of treatment (odds ratios for the lower, middle, and upper tertiles = 1.25, 1.34, and 1.59; P for trend = 0.007).

Conclusion Treatment with ACE-inhibitors might selectively improve cognitive performance in patients with heart failure. However, up-titration of these agents might be required to yield the greatest benefit.

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Introduction

The prevalence and incidence of heart failure (HF) is increasing in Western countries, mostly among subjects older than 80.¹ In recent years, an abnormal prevalence of cognitive dysfunction, ranging from 35 to over 50%, has been described among older subjects with HF.²⁻⁴ Cognitive impairment, in turn, has proved to be a powerful, independent predictor of increased disability and mortality in HF patients.^{5,6}

The aetiology of so-called 'cardiogenic' dementia, formerly attributed to cerebral embolism, is currently ascribed to chronic cerebral hypoperfusion,⁷ resulting from left ventricular systolic dysfunction and systolic arterial hypotension.^{2,3} This is thought to imply a potential reversibility of this form of cognitive impairment, at least before the development of structural cerebral alterations.^{7,8} This issue is crucial from the clinical and economic perspective, as cognitive impairment associated with HF is currently thought to affect over one million people in the US alone, and because even moderate gains in cognitive functioning among these patients might allow substantial reductions of mortality rates and resource consumption.^{6,8} However, despite sparse reports on the effects of pacemaker implantation or cardiac transplantation on cognitive functioning of selected patients,^{9,10} no intervention has yet been identified that might improve cognitive performance in the majority of subjects with HF.

Angiotensin-converting enzyme (ACE)-inhibitors and angiotensin II receptor antagonists have been proved to prevent cognitive decline, or even to reverse cognitive deficits, in hypertensive populations.¹¹⁻¹³ In addition, enalapril has been found to increase cerebral blood flow in patients with HF.¹⁴ On the other hand, systolic blood pressure levels below 130 mmHg have been associated with increased probability of cognitive impairment among hospitalized patients with HF who received vasodilating agents.³ This finding, along with other reports on reduced cerebrovascular reactivity in HF patients, raised concern about the potential detrimental effects of these agents on cerebral perfusion of subjects with HF.¹⁵ We assessed whether starting treatment with ACE-inhibitors during the hospital stay was associated with improving cognitive functioning in 1220 patients with HF enrolled in a multi-centre pharmaco-epidemiology study.

Methods

Data source

We analysed the database of the Gruppo Italiano di Farmaco-epidemiologia nell'Anziano (GIFA), a large collaborative study of adverse drug reactions in hospitalized patients. The methods of the GIFA study have been described in detail elsewhere.¹⁶ Briefly, all patients admitted to the 81 clinical centres (either geriatric or internal medicine hospital wards) throughout Italy in several surveys were enrolled on admission and followed until discharge, without exclusion criteria. For each patient, a

questionnaire was completed on admission and updated daily by a study physician who had received specific training. Data were recorded using dedicated software that automatically linked brand drug names and diagnoses with respective codes;¹⁷ the variables recorded included demographic characteristics, objective tests and measures, drugs taken before admission, during hospital stay and at discharge, and admission and discharge diagnoses. In the present study we analysed data of participants enrolled in 1991, 1993, 1995, and 1997. Among 17 526 participants enrolled during these study years, we excluded 2639 patients who took ACE-inhibitors before hospitalization, and 2806 with missing data for the main study variables. Thus, the study sample included 12 081 participants. In logistic regression analyses, cases with missing data for control (laboratory) variables were treated by the single imputation method.¹⁸ This approach implies substitution of a value (in this case, the variable mean of the complete cases) for each missing value. Indeed, this method underestimates uncertainty for imputed cases, and imputed variables are characterized by smaller standard errors than nominal levels. This could affect the assessment of the role of confounding in multivariable analyses.

Diagnosis of heart failure

The admission diagnosis of HF was verified by the study researchers.⁶ The accuracy of such a diagnosis was tested in the 1993 GIFA survey against a 'definite' diagnosis, based on a validated series of physical and laboratory (e.g. cardiomegaly on chest X-ray) data; using a score ≥ 8 as reference diagnosis,¹⁹ the clinical diagnosis had a specificity $>95\%$.²⁰

Assessment of cognitive function

Cognitive performance was assessed on admission and at discharge using the Hodkinson Abbreviated Mental Test (AMT).²¹ This test has been proved reliable for assessing cognitive functioning in older subjects,²² and has been adopted in epidemiological surveys.²³ Use of this test has also been validated and utilized in Italian populations.^{3,5,6,24} This test can be performed easily and rapidly by non-specialized personnel; it does not need writing or reading tests and is consistent with other screening tests for dementia. The AMT includes 10 items: What is your present age? What year is it? Please count from 20 backwards to 1; What is the time? When is your birthday? Could you repeat the address which I gave you? When did the First World War begin? What is the name of this place? What is the name of the President of the Republic? Can you recognize these... people?. This test explores three cognitive domains: information, memory, and concentration. The score is 1 for each correct answer, and 0 for a wrong answer.

Coding of drugs and diseases

Drugs were coded according to the Anatomical Therapeutic and Chemical codes.¹⁷ Daily dosages were calculated by multiplying the strength of the drug product by the number of daily administrations.²⁵ Diagnoses were coded according to the International Classification of Diseases, Ninth Edition, Clinical Modification codes.²⁶ Co-morbidity was quantified using the Charlson co-morbidity index score by adding scores assigned to specific discharge diagnoses.²⁷ In addition, coronary disease, hypertension, diabetes, renal disease, anaemia, and atrial fibrillation were analysed as separate variables. Patients with diagnosis

Table 1 Characteristics of participants with heart failure by incident use of ACE-inhibitors

	Use of ACE-inhibitors (<i>n</i> = 446) <i>n</i> (%) or mean \pm SD	No use of ACE-inhibitors (<i>n</i> = 774) <i>n</i> (%) or mean \pm SD	<i>P</i>
Demographics			
Age, years	79 \pm 9	79 \pm 9	>0.2
Sex, female	255 (57)	411 (53)	0.17
Education, years	5 \pm 3	5 \pm 3	>0.2
Co-morbid conditions			
Coronary disease	140 (31)	180 (23)	0.002
Hypertension	138 (31)	138 (18)	<0.0001
Atrial fibrillation	120 (27)	176 (23)	0.102
Diabetes	106 (24)	98 (13)	<0.0001
Hepatic disease	8 (2)	26 (3)	0.102
Renal disease	27 (6)	84 (11)	0.005
Co-morbidity score index ³³	2.1 \pm 1.4	2.3 \pm 1.7	0.05
Medications			
Digitalis	357 (80)	528 (68)	<0.0001
Diuretics	405 (91)	561 (73)	<0.0001
Nitrates	229 (51)	315 (41)	<0.0001
Anti-platelets	55 (12)	103 (13)	>0.2
Calcium antagonists	117 (26)	219 (28)	>0.2
Beta-blockers	4 (1)	15 (2)	0.157
Objective tests			
Serum sodium, mmol/L	140 \pm 4	139 \pm 5	0.013
Serum potassium, mmol/L	4.2 \pm 0.6	4.2 \pm 0.7	>0.2
Serum creatinine, μ mol/L	106.08 \pm 44.2	123.76 \pm 79.56	0.001
Serum albumin, g/L	36 \pm 5	36 \pm 6	>0.2
AMT ²⁷	7 \pm 3	7 \pm 3	>0.2
Systolic blood pressure, mmHg	153 \pm 27	140 \pm 26	<0.0001

of cerebrovascular disease, stroke, or Alzheimer's disease were excluded from analyses.

Analyses

Data of continuous variables are presented as mean values \pm SD. Statistical analyses were performed using SPSS for Windows 10.1.0 software. All the tests were two-sided; differences were considered significant at the $P < 0.05$ level. Analysis of variance for continuous variables in relation to use of ACE-inhibitors during hospital stay was performed by ANOVA comparisons; χ^2 analysis was used for dichotomous variables. Adjustment for multiple tests (as depicted in Table 1) was not applied for these comparisons, because the general null hypothesis (that all null hypotheses were true simultaneously) was not of interest to this study, and because the aim of these comparisons was descriptive.²⁸

As the median variation in the AMT score during hospital stay was 0, increases ≥ 1 point in the cognitive performance score were adopted as the main outcome variable. χ^2 analysis was used to assess differences in the variations in cognitive performance according to in-hospital use of ACE-inhibitors among participants with and without diagnosis of heart failure; the homogeneity of odds ratios across these groups was assessed by the Breslow-Day and Tarone's tests. These tests were also applied after stratifying participants according to systolic blood pressure levels below or above 130 mmHg, as measured on admission and at discharge. This cut-off level for blood pressure was chosen because systolic blood pressure levels below 130 mmHg have been recommended in the management of

patients with heart failure,²⁹ and because this level has been found to best predict cognitive impairment in older subjects with heart failure.³ The Breslow-Day and Tarone's tests were also used to assess the homogeneity of odds ratios for the association between use of ACE-inhibitors and improving cognitive performance across the study years among participants with HF. The extent of variations in the AMT score and in blood pressure levels according to the use of ACE-inhibitors was evaluated using the non-parametric Mann-Whitney *U* test. Logistic regression analysis was used among participants with HF to estimate the association of variables of interest, including treatment with ACE-inhibitors, with improved cognitive performance at discharge. Linearity of continuous variables was assessed using the ANOVA test of linearity; the linearity assumption was assumed to be satisfied at a $P < 0.05$ level. To assess independent correlates of variations in cognitive functioning, which might confound the association of treatment with ACE-inhibitors with the outcome variable, groups of variables (demographics, co-morbid conditions, medications, and objective tests) were first examined in separate age- and sex-adjusted regression models with simultaneous introduction of covariates, as depicted in Table 2. Those variables, significant at the $P < 0.1$ level in these initial models, were simultaneously entered into a summary age- and sex-adjusted regression model, further adjusted for the baseline (admission) AMT score (Table 2). The summary model was also analysed after removal of systolic blood pressure.

The effect of dosages and duration of treatment with ACE-inhibitors was assessed using the summary model, with further adjustment for the length of hospital stay. The ANOVA tests evidenced significant linearity and lack of deviation from

Table 2 Association (odds ratios, OR, and 95% confidence intervals, CI) of groups of variables with improved cognitive performance at hospital discharge, as calculated by the initial age- and sex-adjusted logistic regression models, and by the 'summary' model. All the covariates were entered simultaneously into the regression models

	Initial regression models		Summary model ^b	
	OR	95% CI	OR	95% CI
Demographics				
Age, years	1.01	0.99–1.03	0.99	0.98–1.01
Sex, female	0.72	0.54–0.96	0.74	0.56–0.98
Education, years	0.95	0.90–1.01	0.97	0.92–1.03
Co-morbid conditions				
Coronary disease	1.18	0.86–1.59		
Hypertension	1.09	0.78–1.51		
Atrial fibrillation	1.11	0.82–1.50		
Diabetes	1.28	0.89–1.82		
Anaemia ^a	1.48	0.96–2.28		
Renal disease	0.76	0.45–1.26		
Hepatic disease	0.65	0.26–1.62		
Co-morbidity score index ³²	1.06	0.96–1.17		
Medications				
ACE-inhibitors	1.50	1.14–1.98	1.57	1.18–2.08
Calcium antagonists	1.03	0.76–1.39		
Digoxin	1.31	1.12–1.72	1.16	0.98–1.89
Anti-platelets	0.76	0.50–1.16		
Nitrates	1.12	0.86–1.48		
Diuretics	0.77	0.54–1.10		
Beta-blockers	0.77	0.22–2.75		
Objective tests				
Systolic blood pressure, mmHg	0.99	0.99–1.00	0.99	0.98–0.99
Serum sodium, mmol/L	0.99	0.96–1.03		
Serum potassium, mmol/L	0.93	0.74–1.18		
Serum albumin, g/dL	1.34	0.98–1.82	1.4	1.02–1.92
Serum creatinine, 88.4 µmol/L increases	1.03	0.84–1.27		

^aHaemoglobin below 120 g/L among women, or 130 g/L among men.

^bAdjusted for baseline cognitive performance score.

linearity for the correlation of dosages ($P = 0.002$ and $P = 0.630$) and length of treatment ($P = 0.0001$ and $P = 0.93$) with increased AMT score at discharge.

Finally, we analysed, in the summary regression model, the interaction term 'use of ACE-inhibitors * systolic blood pressure', both on admission and at discharge, as well as the interaction term 'use of ACE-inhibitors * study year'.

Results

Patient sample

Among 12 081 patients suitable for analyses during the study years, 1220 had a confirmed diagnosis of HF. According to the design of this study, none of these 12 081 patients received ACE-inhibitors before hospitalization.

Participants with heart failure

The main characteristics, according to incident treatment with ACE-inhibitors, of participants with HF are depicted in *Table 1*. The median length of hospital stay was 13 days (interquartile range 8–20). During hospital

stay, treatment with ACE-inhibitors was started in 446 participants; single agents with respective dosages are depicted in *Table 3*. Systolic blood pressure levels ≥ 130 mmHg were found in 72% of participants who started ACE-inhibitors, but in 85% of those who were not prescribed these agents ($P < 0.0001$). Also, higher dosages were more frequently prescribed to patients with systolic blood pressure ≥ 130 mmHg, as compared with participants with lower blood pressure levels (28 vs. 22%, $P = 0.039$). Among participants with admission systolic blood pressure levels ≥ 130 mmHg, those who received ACE-inhibitors developed greater reduction in blood pressure at discharge (17 ± 26 mmHg), as compared with the remaining subjects (9 ± 23 mmHg; Mann-Whitney U $P < 0.0001$). Among patients with admission systolic blood pressure < 130 mmHg, systolic blood pressure increased by 13 ± 23 mmHg among those treated with ACE-inhibitors, and by 6 ± 16 mmHg among participants who did not receive the treatment (Mann-Whitney U $P = 0.09$). Cognitive impairment, as defined by AMT score < 7 ,^{3,5,6,24} was found in 34% of participants with systolic blood pressure ≥ 130 mmHg, and in 45% of those with lower blood pressure levels ($P = 0.001$).

Table 3 Prevalent use and median dosages of single agents

ACE-inhibitors ^a	n (%)	Daily dosage (mg)
Enalapril	276 (62)	10
Captopril	119 (27)	50
Lisinopril	54 (12)	10
Ramipril	12 (3)	2.5
Fosinopril	6 (1)	20
Quinapril	5 (1)	10

^aSwitching between agents was recorded in 20 participants.

Use of ACE-inhibitors and improvement in cognitive functioning according to diagnosis of heart failure

Among 1220 subjects with HF, increased AMT scores at discharge were observed in 133/446 (30%) patients who received ACE-inhibitors, and in 167/774 (22%) subjects who were not dispensed such agents ($P = 0.001$). Among the 10 861 participants in the GIFA database without heart failure, improved cognitive performance was found in 19% (214/1153) of participants who started treatment with ACE-inhibitors, and in 18% (1753/9708) of the remaining subjects ($P = 0.675$). The Breslow–Day and Tarone’s tests confirmed ($P = 0.011$) that the association between incident use of ACE-inhibitors and improved cognitive performance differed according to the diagnosis of HF.

Use of ACE-inhibitors and variations in cognitive functioning among participants with heart failure

According to the Mann–Whitney U test, the observed increase in the AMT score during hospital stay was greater among subjects who started ACE-inhibitors, compared with untreated participants (mean values 0.37 ± 0.48 vs. 0.20 ± 1.6 , respectively; median values and interquartile ranges 0, 0 to 0, and 0, 0 to 1, respectively; Mann–Whitney U $P = 0.009$). The Breslow–Day and Tarone’s tests did not support the hypothesis of a different effect of ACE-inhibitors on the probability of improved cognitive functioning according to admission ($P = 0.777$) or discharge ($P = 0.298$) systolic blood pressure levels below or above 130 mmHg. Also, these tests did not confirm ($P = 0.19$) the hypothesis of a variation in the effect of ACE-inhibitors on improving cognition across the study years.

In the initial age- and sex-adjusted logistic regression models, sex, education, use of ACE-inhibitors and digoxin, systolic blood pressure, and albumin serum levels were associated with improvement in cognitive performance at a $P < 0.1$ level (Table 2). When these variables were entered simultaneously in the summary age- and sex-adjusted regression model, use of ACE-inhibitors was still associated with improved cognition (OR = 1.57; 95% CI 1.18–2.08), after adjusting for potential confounders and baseline AMT score (Table 2). The association

between use of ACE-inhibitors and improved AMT score also persisted when systolic blood pressure was not entered into the summary model (OR = 1.49; 95% CI 1.12–1.96).

In the same summary regression model, analysis of the interaction term confirmed that the association between use of ACE-inhibitors and improvement in cognitive functioning did not vary according to admission or discharge systolic blood pressure levels ($P = 0.771$, and $P = 0.393$, respectively), nor across the study years ($P = 0.632$).

The effect of single agents could not be analysed due to the insufficient sample power of strata.

Effect of dosages and duration of treatment

In the summary logistic regression model, use of increasing dosages of ACE-inhibitors was associated (P for trend = 0.001) with increasing probability of improving cognitive functioning (Figure 1). Also, in the summary regression model, further adjusted for the length of hospital stay, increasing tertiles of duration of treatment were associated (P for trend = 0.007) with increasing probability of improved cognitive performance at discharge (Figure 2).

Discussion

Results of our study indicate that starting treatment with ACE-inhibitors during hospital stay is independently associated with improvement in cognitive performance among patients with HF. Noticeably, this association was not found among subjects without diagnosis of HF. The probability of improving cognitive performance increases with increasing duration of treatment, and with use of higher dosages. Even though systolic arterial hypotension has been associated with increased probability of cognitive impairment among patients with HF, the association between use of ACE-inhibitors and improvement in cognitive performance seems to be independent of blood pressure levels, either before or during treatment.

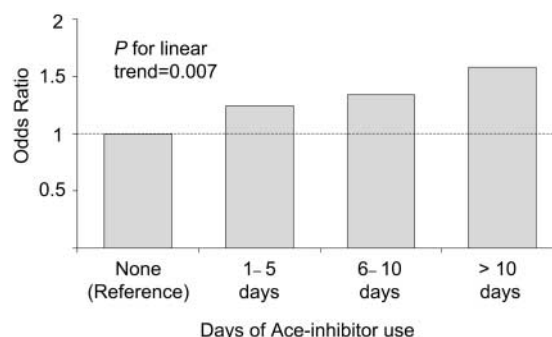


Figure 1 Adjusted probability (OR with 95% CI) of improving cognitive performance associated with ACE-inhibitor dosages equal to or below ('low dose') or above ('high dose') the median values, as indicated in Table 3. Probabilities were calculated using the 'summary' regression model, as depicted in Table 2.

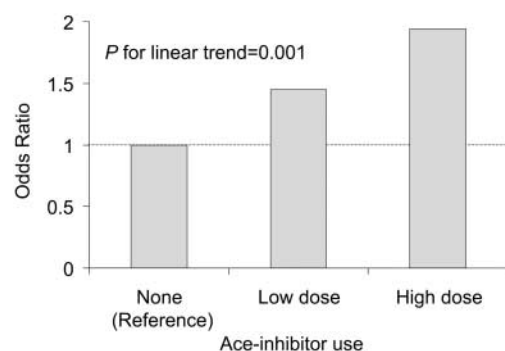


Figure 2 Adjusted probability of improving cognitive functioning according to increasing tertiles of duration of treatment. Probabilities were calculated using the 'summary' regression model (Table 2), further adjusted for the length of hospital stay.

The prevalence of HF is rising in Western countries, particularly among older subjects.¹ At present, the prognosis of HF in elderly patients remains poor.³⁰ In addition, HF currently represents the single most costly cardiovascular disease in the United States, chiefly because of the high prevalence of associated disability.³¹ Several analyses have found that as many as 30–50% of patients with HF have cognitive dysfunction.^{2–4} Cognitive impairment, in turn, has been associated with a five-fold increase in the risk of mortality,⁶ and a six-fold increase in the probability of dependence for the activities of daily living among older patients with HF.⁵ Noticeably, cognitive dysfunction, even when mild, is a known determinant of disability in general, older populations.³² Also, the observed association of cognitive dysfunction with mortality among elderly subjects with HF is in keeping with the prognostic impact of cerebral metabolic abnormalities evidenced in younger patients screened for heart transplantation.³³ Given the substantial clinical and economic impact of cognitive impairment associated with HF, the search for effective strategies to reduce the prevalence of 'cardiogenic dementia' has to be considered a matter of public health interest.⁸

At present, cerebral hypoperfusion, rather than cerebral embolism, is thought to represent the major cause of cognitive impairment in older patients with HF.⁷ Autoregulation of cerebral circulation is impaired in older age.³⁴ In addition, HF is associated with reduced cerebrovascular reactivity, even in younger patients.³⁵ In recent years, several reports on the association of cognitive impairment with both left ventricular dysfunction and systolic hypotension in older patients with HF have revived the old concept of so-called 'cardiogenic' or 'circulatory' dementia.⁷ The neuropathological substrate of this clinical entity, chiefly characterized by impairment in calculation and visuo-spatial intelligence,^{2,8} seems to be represented by white matter alterations, in the setting (common to several conditions of chronic cerebral hypoperfusion) of 'subcortical vascular dementia'.^{8,36}

Two small studies have shown that cognitive impairment is reversible among patients who undergo either pacemaker implantation or cardiac transplantation.^{9,10}

However, despite the increasing evidence regarding the extent and prognostic impact of cerebral involvement in patients with HF,^{6,33} cognitive functioning is generally not assessed in these subjects. For instance, the reported prevalence of any diagnoses of cognitive impairment (thus including Alzheimer's disease) in a recent large study of older Medicare patients with HF was as low as 9%.³⁷ The result is that, in the vast majority of patients, there is no information about the effects of standard pharmacotherapy for HF on cognitive functioning. In this setting, the finding of increased probability of cognitive impairment among older subjects with HF whose systolic blood pressure levels were lower than 130 mmHg has suggested that vasodilating treatment might aggravate cerebral hypoperfusion among older and 'frailer' patients.^{3,7,8,15} Our results indicate that, among older patients with HF, the association between use of ACE-inhibitors and improving cognitive performance does not vary according to systolic blood pressure levels either before, or during, treatment.

Due to its observational design, the present study does not allow us to unequivocally establish a direct role of ACE-inhibitors on cognitive functioning, as only a randomized trial might rule out the role of confounders. Also, results of the present study do not allow the identification of the pathophysiological pathway involved in the observed effect of ACE-inhibitors on cognitive functioning of patients with HF. Treatment with ACE-inhibitors can improve left ventricular systolic function,³⁸ which might increase cerebral perfusion. In addition, HF is associated with increased angiotensin II activity in the brain; in turn, angiotensin II is known to produce endothelial dysfunction in the cerebral circulation.³⁹ In keeping with these observations, enalapril has been found to increase cerebral blood flow in patients with HF.¹⁴ Indeed, such a 'circulatory' hypothesis for the cerebral activity of ACE-inhibitors in HF might explain the rapid onset, as well as the selectivity of the effects of these agents on cognitive functioning of participants with HF in this study.

Our finding (Figure 1) of a dose-related effect of ACE-inhibitors on cognitive functioning in older patients with HF is also of interest. In this (Table 3), as well as in other studies on older populations with HF,⁴⁰ most subjects were found to receive lower dosages than those acknowledged by randomized clinical trials. Such a prescribing attitude might reflect some uncertainty about the efficacy and safety of high-dose treatment of elderly subjects with HF. Indeed, several observations failed to demonstrate any clear advantage of high-dose ACE-inhibitor therapy, compared with low dosages, regarding survival and hospitalization rates in HF patients.⁴¹ Our results suggest that up-titration of ACE-inhibitors yielded the greatest increases in cognitive performance among HF patients with cognitive impairment, who are at higher risk for disability and earlier mortality. Indeed, the beneficial effects of ACE-inhibitors on cognitive functioning are probably underestimated in the present study, considering both the limited length of observation, and the evidence of a time-dependent effect of these agents (Figure 1).

Noticeably, participants who received ACE-inhibitors in the present study were sicker than untreated patients, and, as suggested by more intensive treatment with digitalis, diuretics, and nitrates (Table 1), with more severe HF. This conservative bias further supports the hypothesis of a favourable effect of ACE-inhibitors on cognitive functioning of frailer patients.

In a more general setting, results of this study highlight the inadequacy of mortality and re-admission rates as the only outcome variables to be considered in the management of patients with HF. Several authors have outlined the need for health outcomes research in populations with HF, aiming at generating evidence that might support clinical decision making, improve clinical practice, and guide health policy.^{15,30,31,42} Focusing on health status outcomes would also be consistent with the Institute of Medicine's promotion of patient-centred care, among the six strategies designated to improve the quality of care in the US.⁴³ Our results confirm the potential role of cognitive functioning among the primary treatment outcomes in HF, highlighting the importance of systematic neuropsychological evaluation in the assessment and treatment of patients with HF, both in clinical practice and research.

Acknowledgements

The GIFA study was partially supported by a grant from the National Research Council (n.94000402).

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