European Journal of Pharmacology 628 (2010) 164–170

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Cardiovascular Pharmacology

Chronic heart failure patients with high collagen type I degradation marker levels benefit more with ACE-inhibitor therapy

Sofia V. Chatzikyriakou [a], Dimitrios N. Tziakas [a,*], Georgios K. Chalikias [a], Dimitrios Stakos [a], Adina Thomaidi [a], Konstantina Mitrousi [a], Harisios Boudoulas [b]

[a] University Cardiology Department, Medical School, Democritus University of Thrace, Alexandroupolis, Greece
[b] Center for Clinical Research, Foundation of Biomedical Research, Academy of Athens, Athens, Greece

ARTICLE INFO

Article history:
Received 7 May 2009
Received in revised form 12 November 2009
Accepted 23 November 2009
Available online 1 December 2009

Keywords:
Angiotensin converting enzyme-inhibitor
Collagen metabolism
Prognosis
Chronic heart failure

ABSTRACT

Not all patients respond to angiotensin converting enzyme (ACE)-inhibitor equally. Genetic or other phenotypic variations might be useful in predicting the therapeutic efficacy of these drugs. With the present study we assessed the prognostic impact of ACE-inhibitor in chronic heart failure patients with different degrees of collagen metabolism as assessed by serum levels of a collagen type I degradation marker (CITP). One hundred ninety-six (126 male, 69 ± 10 years) chronic heart failure patients were studied prospectively for 12 months regarding survival. Serum concentrations of CITP were measured at study entry. Chronic heart failure patients were divided into groups according to whether ($n = 114$) or not ($n = 82$) they received ACE-inhibitor as well as to their CITP levels. Survival (52.2%) was significantly lower in ACE-inhibitor naive patients with high CITP levels compared to ACE-inhibitor naive patients with low CITP levels (83.3%, $P = 0.003$), to ACE-inhibitor users with low CITP levels (80%, $P = 0.006$) and to ACE-inhibitor users with high CITP levels (70.4%, $P = 0.015$). ACE-inhibitor related improvement in mortality was most predominant in chronic heart failure patients with high CITP levels. CITP levels possibly reflecting an activated status of the renin–angiotensin–aldosterone system, may be of clinical relevance since they identify a subgroup of patients that is more susceptible to treatment with an ACE-inhibitor.

1. Introduction

The effectiveness of angiotensin converting enzyme (ACE)-inhibitors in improving survival of patients with chronic heart failure has been reported from recent large-scale clinical trials (Garg and Yusuf, 1995). However, despite optimized treatment with ACE-inhibitors, a group of patients with chronic heart failure is characterized by a greater benefit in survival (Van de Wal et al., 2006; Roig et al., 2000). This observation suggests that not all patients respond to ACE-inhibitors equally (Dickerson et al., 1999; Struthers et al., 2001), and therefore it has been postulated that genetic or other phenotypic variations might be useful in predicting the therapeutic efficacy of these drugs (Jan Danser et al., 2007).

There is accumulating data showing that angiotensin modulates collagen synthesis and degradation (Gonzalez et al., 2002). This evidence has supported the concept that beneficial effects of ACE-inhibitors on prognosis in these patients are related, at least in part, to their effects on myocardial remodelling and especially on collagen metabolism and fibrosis (Landmesser et al., 2009; Zannad and Radauceanu, 2005; Fleming, 2006).

In addition, non-invasive measurement of collagen-derived serum peptides has been proposed as a useful tool to address myocardial fibrosis from a distance (Weber, 1997; Zannad et al., 2001). Recent studies have also shown that collagen turnover—as assessed with serological markers—is altered in chronic heart failure and has an impact on prognosis (Klappacher et al., 1995; Kitahara et al., 2007; Zannad et al., 2000). In specific high collagen type I degradation levels were negatively associated with survival (Klappacher et al., 1995; Kitahara et al., 2007; Zannad et al., 2000).

We hypothesized that the extent of collagen metabolism, as assessed by serum levels of a collagen type I degradation marker, would provide insight into the impact that ACE-inhibitor treatment has on survival in chronic heart failure patients.

2. Material and methods

2.1. Patients

We prospectively studied 207 consecutive patients, who were admitted to the Coronary Care Unit, Department of Cardiology, with acute decompensation of chronic heart failure. The chronic heart failure status had been determined on a prior visit to our Outpatient Heart Failure Clinic.

Patients were followed for up to 12 months after admission using a standardized protocol that included outpatient visits and telephone

* Corresponding author. Voulgaroktonou 23, 68100 Alexandroupolis, Greece. Tel.: +30 25510 35596(home), +30 25510 76205(office); fax: +30 25510 76245.
E-mail address: dtziakas@med.duth.gr (D.N. Tziakas).

0014-2999/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2009.11.047

contacts. Follow up contacts were focused on the recording of ACE-inhibitor treatment adherence. Patients who discontinued ACE-inhibitor therapy ($n=6$) were excluded. Furthermore, patients who failed to attend follow up visits ($n=3$) or had incomplete follow up data ($n=2$) were also excluded from further analysis. The remaining 196 patients (126 male, mean age 69 ± 10 years) constituted the study group. The endpoint of the study was cardiac death defined as death from worsening heart failure or sudden cardiac death.

Chronic heart failure patients were divided into groups according to whether or not they received ACE-inhibitor therapy. Since treatment of study participants was in agreement with current published guidelines, restraining patients from ACE-inhibitor therapy was solely based on specific treatment contraindications/side-effects (Dickstein et al., 2008). Although chronic heart failure patients who were not on ACE-inhibitors fulfilled similar diagnostic criteria as chronic heart failure patients receiving such therapy (Table 1), they were more likely to have

Table 1
Comparison of baseline characteristics between angiotensin converting enzyme (ACE)-inhibitor treated and naive chronic heart failure patients.

Variable	ACE-inhibitor naive patients $n=82$	ACE-inhibitor treated patients $n=114$	*P*
Age, years	68 (65–70)	68 (66–70)	0.812
Male/Female, *n*	52/30	74/40	0.880
Systolic blood pressure, mm Hg	120 (113–127)	146 (141–151)	<0.001[a]
Heart rate, bpm	84 (80–88)	74 (71–77)	<0.001[a]
QRS duration, s	0.11 (0.10–0.12)	0.10 (0.09–0.11)	0.143
Body mass index (kg/m^2)	29 (28–30)	30 (29–31)	0.267
NYHA classification, n (%)			0.062
II	22 (27%)	42 (37%)	
III	42 (51%)	60 (53%)	
IV	18 (22%)	12 (10%)	
Etiology, n (%)			0.056
Coronary artery disease	34 (42%)	50 (44%)	
Hypertensive cardiomyopathy	14 (17%)	34 (30%)	
Valve disease	14 (17%)	16 (14%)	
Idiopathic dilated cardiomyopathy	20 (24%)	14 (12%)	
Co-morbidities, n (%)			
Diabetes mellitus	32 (39%)	52 (46%)	0.383
Hypertension	46 (56%)	78 (68%)	0.098
Atrial fibrillation	36 (44%)	54 (47%)	0.665
Smoking	14 (17%)	26 (23%)	0.372
Respiratory disease	34 (41%)	38 (33%)	0.244
Echocardiographic findings			
Preserved systolic function, *n* (%)	12 (15%)	36 (32%)	0.007[b]
Left ventricular mass, g	387 (360–414)	412 (381–442)	0.600
Left ventricular ejection fraction, %	36 (34–39)	42 (40–45)	0.002[a]
Treatment during follow up, n (%)			
b-Blockers	12 (15%)	26 (23%)	0.200
Diuretics	82 (100%)	114 (100%)	1.000
Aldosterone antagonists	26 (32%)	38 (33%)	0.878
Digitalis	32 (40%)	56 (49%)	0.242
Nitrates	44 (54%)	58 (51%)	0.772
Angiotensin receptor blockers	20 (24%)	6 (5%)	<0.001[b]
Calcium channel blockers	16 (20%)	30 (26%)	0.308
Amiodarone	12 (15%)	12 (11%)	0.388
Statins	26 (32%)	48 (42%)	0.179
Aspirin	34 (42%)	62 (54%)	0.083
Clopidogrel	16 (20%)	12 (11%)	0.098
Anticoagualants	30 (37%)	54 (48%)	0.145
Biochemical markers			
Hemoglobin, g/dl	12.9 (12.6–13.3)	13.3 (13–13.6)	0.084
White blood count, x10^3/μl	8.6 (8–9.2)	8.7 (8.3–9.2)	0.746
Creatinine, mg/dl	1.3 (1.2–1.4)	1.2 (1.2–1.3)	0.314
Sodium, mg/dl	140 (139–142)	142 (141–142)	0.059
Uric acid, mg/dl	7.7 (7.3–8)	7.6 (7.3–7.9)	0.808
Albumin, g/dl	6.8 (6.7–6.9)	6.7 (6.6–6.8)	0.543
Total cholesterol, mg/dl	162 (150–173)	173 (164–182)	0.120
HDL cholesterol, mg/dl	44 (41–46)	45 (43–48)	0.480
Triglycerides, mg/dl	124 (108–139)	142 (114–170)	0.311
Glomerular filtration rate, ml/min/1.73 m^2	67 (61–72)	69 (64–73)	0.591
CRP, mg/dl	1.6 (1.3–2)	1.6 (1.3–2)	0.460
CITP, ng/ml	0.55 (0.44–0.66)	0.43 (0.37–0.49)	0.034[a]
NT-proBNP, pg/ml	6327 (4100–8554)	2723 (2141–3306)	0.003[a]

Values are expressed as means and 95% CI for continuous variables and as number of patients and % for categorical variables.
ACE; angiotensin converting enzyme, CI; confidence intervals, CITP; carboxy-terminal telopeptide of collagen type I, CRP; C-reactive protein, HDL; high density lipoprotein, NT-proBNP; N-terminal propeptide of brain natriuretic peptide, and NYHA; New York Heart Association.
[a] For unpaired Student's *t*-test.
[b] For chi-square test.