Clinical Trials

Efficacy and Safety of Angiotensin-Converting Enzyme Inhibitors in Patients With Left Ventricular Systolic Dysfunction and Hyponatremia

LOUISE BALLING, MD,[1] LARS KOBER, MD, DMSc,[1,3] MORTEN SCHOU, MD, PhD,[1] CHRISTIAN TORP-PEDERSEN, MD, DMSc,[2,3] AND FINN GUSTAFSSON, MD, PhD, DMSc[1,3]

Copenhagen and Gentofte, Denmark

ABSTRACT

Background: The presence of hyponatremia has been perceived to increase the risk of adverse events on initiation of treatment with angiotensin-converting enzyme inhibition in heart failure patients. The aim of this study was to investigate if baseline hyponatremia (plasma Na^+ <135 mmol/L) predicts development of hypotension and renal impairment in patients with myocardial infarction (MI) and left ventricular dysfunction (LVD) treated with angiotensin-converting enzyme inhibitors.

Methods and Results: A retrospective analysis was performed with data from the Trandolapril Cardiac Evaluation (TRACE) a double-blind randomized study. Plasma sodium levels were available in 1,731 patients, who were considered as the study population. Patients 3−7 days after MI with left LVD (LVEF ≤0.35), were randomized to trandolapril (n = 876) or placebo (n = 873). Baseline hyponatremia did not predict development of hypotension or worsening renal function after 1 month in patients treated with trandolapril compared with placebo (122 ± 19.1 mm Hg vs 123.2 ± 20.4 mm Hg [P = .84]; and creatinine clearance 57.4 ± 21.4 mL/min vs 55.2 ± 21.0 mL/min [P = .8]). There was no interaction between hyponatremia and the effect of trandolapril (P = .68).

Conclusions: Mild hyponatremia was not a contraindication for the initiation of treatment with angiotensin-converting enzyme inhibitors in patients with post-MI heart failure. (*J Cardiac Fail 2013;19:725−730*)

Key Words: ACE-I, hyponatremia, heart failure.

Treatment with angiotensin-converting enzyme inhibitors (ACE-I) has been repeatedly documented to improve survival and morbidity in patients with heart failure (HF) with reduced ejection fraction (HFrEF) as well as in patients with recent myocardial infarction (MI) and reduced left ventricular systolic function.[1−8] Therefore, ACE-I therapy is a cornerstone in the treatment of HF.[9,10] Hyponatremia, often defined as plasma sodium concentration (plasma Na^+) <135 mmol/L, is a common finding in HF, present in up to 20%−30% of patients with more advanced HF.[11−13] The presence of hyponatremia in HF patients has been known to increase the risk of adverse events upon initiation and treatment with ACE-I because of a risk of hypotension and renal dysfunction.[13−15]

Data from randomized clinical trials evaluating the risks or benefits associated with initiation of ACE-I in hyponatremic patients with HF are not available. Using data from

From the [1]Heart Center, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [2]Department of Cardiology, Gentofte Hospital, Gentofte, Denmark and [3]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

Manuscript received February 21, 2013; revised manuscript received September 4, 2013; revised manuscript accepted September 11, 2013.

Reprint requests: Louise Balling, MD, The Heart Center, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, Copenhagen, Denmark. Tel: 0045 3545 2142; Fax: 0045 35457705. E-mail: louise.balling@gmail.com

Funding: The Copenhagen University Hospital Research Foundation, Copenhagen University, Hospital Research Foundation and Heart Center Research Foundation at Copenhagen University Hospital. The TRACE study was supported by grants from Abbott Laboratories, Roussel-Uclaf, and Knoll.

See page 729 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2013.09.004

a large randomized trial, the aim of the present study was to investigate if baseline hyponatremia predicts adverse events after 1 month of treatment with the ACE-I trandolapril in patients with a recent MI and left ventricular dysfunction (LVD). The secondary aim was to investigate if there was any interaction between baseline plasma sodium and the effect of trandolapril on long-term mortality.

Methods

A retrospective analysis was performed with the use of data from the Trandolapril Cardiac Evaluation Study (TRACE), a randomized, double-blinded, placebo-controlled trial of trandolapril versus placebo treatment in 1,749 patients with recent acute myocardial infarction and echocardiographic evidence of LVD. All consecutive patients >18 years of age, hospitalized with an enzyme-verified acute MI, were screened in 27 Danish Centers from 1993 to 1996. MI was defined as chest pain or electrocardiographic changes typical of infarction or ischemia in combination with an enzyme increase of ≥2 times the upper normal limit of the local hospital laboratory. Inclusion criteria included an MI 3−7 days before screening and left ventricular (LV) wall motion index (WMI) ≤1.2, corresponding approximately to a LVEF ≤0.35. Both symptomatic and asymptomatic patients with LVD were included in the study. Baseline data were recorded for all included patients. Severe hyponatremia (plasma Na^+ <125 mmol/L) or plasma creatinine >200 μmol/L were exclusion criteria for the TRACE study. Exclusion criteria were an absolute or relative contraindication to ACE inhibition or a definite need for ACE inhibition, severe uncontrolled diabetes mellitus or hypertension, and/or unstable angina pectoris leading to acute coronary angiography. The remaining exclusion criteria have been described in detail previously.[16] After giving informed consent, patients were treated with a 0.5 mg test dose of trandolapril. If the test dose was tolerated, patients were randomized to trandolapril or placebo. Fourteen patients (0.8%) did not tolerate the test dose or suffered from other complications of MI and were excluded from the trial. Up-titration was performed according to protocol up to the maximum dose of 4 mg or the maximal tolerated dose. The mean follow-up time was 26 months (25−50 months). The primary end point was all-cause mortality. Secondary end points were sudden death, cardiovascular mortality, reinfarction, development of severe or resistant heart failure, and a change in left ventricular function (estimated by WMI). Time to death was chosen as efficacy end point, and creatinine clearance and systolic hypotension (defined as systolic blood pressure <100 mm Hg) at day 30 as safety end points. The TRACE study has been described in detail previously.[4,17−20]

Plasma sodium values were available in 1,731 patients, who were considered as the study population for the present retrospective analysis. Plasma sodium was measured in a venous blood sample at the baseline visit of the trial and again at follow-up 1 month after initiation of the study medicine. No patients had severe hyponatremia (plasma Na^+ <125 mmol/L) on the days immediately before randomization, because this would have led to exclusion at the time of screening, but some patients had developed hyponatremia between the time of screening and initiation of treatment with trandolapril or placebo, and per protocol this did not lead to exclusion of the patients. Systolic blood pressure and plasma creatinine, as well as other variables, were measured at baseline and at follow-up 1 month after initiation of the study medication. Additional measurements were done after 3 months and every 3 months until the end of study. Hypotension was defined as a systolic blood pressure <100 mm Hg. Worsening renal function was defined as a decrease of >20% in creatinine clearance at 1 month from baseline.

All patients had given informed consent before participation in the study. The study was approved by the relevant Danish Ethical Committees.

Statistical Analysis

Descriptive data are presented as numbers (n), percentages (%), and means (±SD) as appropriate. Patient characteristics according to the presence of normo- or hyponatremia and the allocated treatment and placebo groups were compared with the use of the χ^2 square test for discrete variables, and continuous variables were compared with the use of the Wilcoxon rank test. All mortality analyses were performed with the use of the intention-to-treat principle. Hazard ratios (HRs) for mortality were compared with the use of Cox proportional hazards regression and are presented with 95% confidence intervals (CIs). All calculations were performed for plasma Na^+ <135 mmol/L as well as for plasma Na^+ values >135 mmol/L. Interaction analyses were carried out by adding an interaction term to the Cox regression model. Time-to-event analyses were performed with the use of the Kaplan-Meier method. All statistical analyses were performed with the use of SAS Statistics version 9.2 (SAS Institute, Cary, North Carolina). The level of significance was defined as $P < .05$.

Results

Patient Characteristics

A total of 1,731 patients were included in this retrospective analysis of the TRACE study. The mean sodium concentration was similar in the trandolapril and placebo groups (137.7 ± 3.6 mmol/L vs 137.5 ± 3.6 mmol/L; $P = .26$). At baseline, 286 patients had hyponatremia (plasma Na^+ <135 mmol/L) and 1,436 patients were normonatremic (plasma Na^+ 135 mmol/L to <145 mmol/L). Mild hyponatremia (plasma Na^+ 130 mmol/L to <135 mmol/L) was present at baseline in 123 patients (7.1%) in the placebo group versus 110 patients (6.4%) in the trandolapril group. Nine patients had hypernatremia (plasma Na^+ ≥145 mmol/L). Baseline characteristics for normonatremic versus hyponatremic patients are presented in Table 1. The presence of hyponatremia was associated with more comorbidity because the hyponatremic patients were significantly older and had a higher prevalence of diabetes, atrial fibrillation, and history of HF compared with normonatremic patients ($P < .0001$). Patients with hyponatremia were treated more often with diuretics than normonatremic patients ($P < .0001$). There were no differences in age, creatinine clearance, or body mass index (BMI) between patients treated with trandolapril or placebo at baseline for all patients (data not shown).

Effect of ACE-I on Blood Pressure and Renal Function in Hyponatremia

Baseline hyponatremia did not predict development of hypotension at 1 month in patients treated with