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## Efficacy of Tolvaptan in Patients Hospitalized for Heart Failure With Refractory Hyponatremia. Clinical Experience in Daily Practice

### Eficacia de tolvaptán en pacientes ingresados por insuficiencia cardíaca e hiponatremia refractaria. Experiencia en la práctica clínica diaria

#### To the Editor,

Hyponatremia (plasma sodium  $\leq 135$  mEq/L) is one of the most common electrolyte abnormalities in patients with acute heart failure (HF) and is considered a marker of poor prognosis.<sup>1</sup>

The latest European Society of Cardiology, Guidelines for HF included tolvaptan, a vasopressin  $V_2$ -receptor blocker that inhibits free water reabsorption,<sup>2</sup> as a valid treatment for patients with refractory hyponatremia.<sup>3</sup>

We present our experience with tolvaptan for the treatment of refractory hyponatremia in patients admitted by HF.

A retrospective study was conducted in patients treated with tolvaptan who were admitted for HF between February 2011 and August 2012 with refractory hyponatremia (sodium  $< 135$  mEq/L despite “classic” treatment, mainly fluid intake restrictions and/or administration of hypertonic saline solution) and persistent symptoms of HF.

Plasma sodium, potassium, and creatinine concentrations, glomerular filtration rate (calculated by the Modification of Diet in Renal Disease equation), weight, and excretion rhythm at the start of tolvaptan therapy were assessed 24 h and 48 h after tolvaptan was given.

The ESTATA/SE 11.1 software package was used for the statistical analysis.

A total of 30 patients (57% women; mean age,  $72 \pm 14$  years) were included. The most common cause of HF (33% of all patients) was ischemic heart disease; 54% of patients presented ventricular dysfunction (mean ejection fraction,  $48 \pm 16\%$ ). All were following optimal treatment for HF and all were receiving diuretic therapy at home.

Treatment was started at a daily dose of 15 mg of tolvaptan in 90% of patients and 30 mg in all others. At the start of treatment, sodium was  $129 \pm 3$  mEq/L. Natremia was significantly increased at 24 h, an effect that persisted at 48 h ( $129 \pm 3$  mEq/L at baseline;  $134 \pm 3$  mEq/L at 24 h;  $135 \pm 3$  mEq/L at 48 h;  $P < .001$ ) (Fig. 1). No significant changes were observed in potassium concentrations after the drug was administered ( $4 \pm 0.5$  mEq/L at baseline;  $4 \pm 0.4$  mEq/L at 24 h;  $4.2 \pm 0.4$  mEq/L at 48 h;  $P > .05$ ).

After treatment, diuresis was significantly increased at 24 h, and the effect was maintained at 48 h ( $80 \pm 45$  mL/h,  $138 \pm 60$  mL/h, and  $136 \pm 64$  mL/h, respectively;  $P < .001$ ) (Fig. 2). Likewise, a significant decrease in patient weight was observed at 48 h ( $67.1 \pm 17.8$  kg vs  $64.1 \pm 15.1$  kg;  $P = .01$ ).

No statistically significant differences were observed in creatinine ( $1.3 \pm 0.5$  mg/dL at baseline;  $1.4 \pm 0.4$  mg/dL at 24 h;  $1.6 \pm 1.1$  mg/dL at 48 h;  $P > .05$ ) or Modification of Diet in Renal Disease ( $54 \pm 20$ ,  $50 \pm 16$ , and  $50 \pm 18$  mL/min/1.73 m<sup>2</sup>, respectively;  $P > .05$ ).

Patients who presented moderate-to-severe hyponatremia (sodium  $< 130$  mEq/L) showed a larger post-treatment increase in natremia and excretion rhythm than those who presented mild

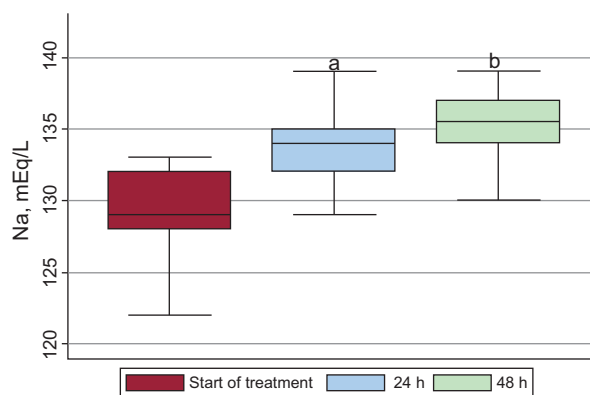
hyponatremia. These results were similar in patients with ventricular dysfunction or HF with preserved systolic function.

The only adverse event occurred in a patient with no known renal impairment who experienced acute renal failure while receiving treatment and it resolved without dialysis.

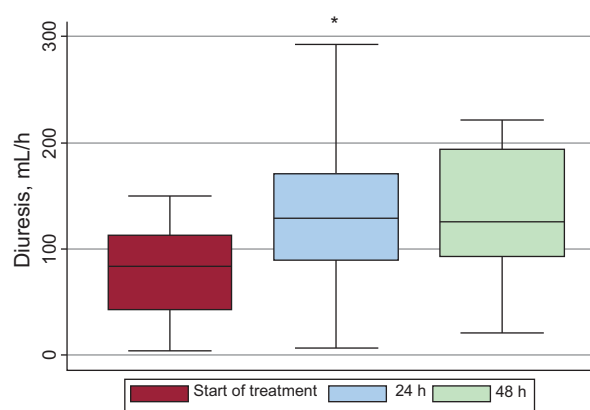
In patients with HF, a significant relationship between natremia and in-hospital mortality was observed, along with an increase in readmissions and long-term morbidity and mortality.<sup>1,2</sup>

Various mechanisms promote this hyponatremia: increased vasopressin due to low cardiac output and decreased renal blood flow, increased perception of thirst, and the use of diuretics.

In patients admitted to our hospital for HF and refractory hyponatremia, we observed a significant increase in the natremia after tolvaptan therapy. Additionally, patients with lower sodium were those who most benefited from treatment, as shown in other studies.<sup>4–6</sup> Our study also observed a significant increase in the excretion rhythm and a decrease in weight without significant decline in kidney function or potassium levels,



**Figure 1.** Course of natremia after tolvaptan therapy in patients with acute heart failure and refractory hyponatremia. <sup>a</sup> $P < .05$  (natremia at the start of treatment vs natremia at 24 h). <sup>b</sup> $P < .05$  (natremia at 24 h vs natremia at 48 h).



**Figure 2.** Course of diuresis after tolvaptan therapy in patients with acute heart failure and refractory hyponatremia. <sup>\*</sup> $P < .05$  (diuresis at the start of treatment vs diuresis at 24 h).

suggesting, that tolvaptan may be a therapeutic option that can be added to loop diuretics, which already have a hyponatremic effect of their own.

Furthermore, our results show similar effects in patients with or without ventricular dysfunction, an important fact taking into account that the prevalence of hyponatremia is similar in both groups.

Therefore, tolvaptan administration in unselected patients with decompensated HF and symptomatic refractory hyponatremia significantly increases sodium concentrations and excretion rhythm without significantly affecting kidney function.

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## Subclinical Coronary Atherosclerosis Identified by Coronary Computed Tomography Angiography in Asymptomatic Population by Coronary Artery Disease Risk Level

### Enfermedad coronaria subclínica por tomografía computarizada multidetector en población asintomática estratificada por nivel de riesgo coronario

#### To the Editor,

Coronary atherosclerosis is a significant cause of death in the developed world that quite frequently presents as a fatal event, hence the interest in detecting it in its subclinical stages.<sup>1</sup> In practice, risk stratification scales are used in population-wide screening to enable us to initiate primary prevention measures. In some parts of Spain, an adapted Framingham scale has been developed,<sup>2</sup> which facilitates screening for high- and low-risk patients. However, it has known limitations in screening low to intermediate-risk patients, for whom other approaches to stratification (biomarkers, imaging techniques) are more useful. In particular, detecting and quantifying coronary wall calcium with multidetector computed tomography (MDCT) has been shown to increase the predictive value of risk scores in asymptomatic patients at intermediate risk but fails to identify patients with noncalcified atherosclerosis.<sup>3</sup>

Our objective was to determine the prevalence of subclinical coronary disease by using noninvasive coronary angiography (NCA) with MDCT in asymptomatic patients and associate this with the adapted Framingham-REGICOR scale of coronary risk levels.

From 2004 thru 2011, we studied 207 consecutive patients (160 men) in the Mediterranean area of Spain who were asymptomatic, aged from 33 to 75 (mean, 54.6 [10]) years, and undergoing a voluntary general check-up including NCA-MDCT (Toshiba Aquilion 64 or 320 detector CT systems). Mean follow-up was 28 (26.4) months.

Atherosclerotic plaques (AsP) were identified in 110 patients (53%; 95% confidence interval [95%CI], 49.6%–60.9%), with 1 vessel

affected in 33/110 (30%), 2 vessels in 37/110 (33.6%) and 3 vessels in 40/110 (36.3%). The left main coronary artery was involved in 33/110 patients, left anterior descending artery in 101/110, circumflex artery in 48/110, and right coronary artery in 75/110 patients. In 22/110 (20%), AsP were not calcified. We found significant luminal obstruction ( $\geq 70\%$ ) in 13/110 patients (11.8%), with no calcification in 2 of them. In the group with AsP, 52/110 (47.2%) patients were young (men aged  $\leq 55$  or women aged  $\leq 65$  years), with noncalcified plaques in 17/52 (32.6%). The patients with AsP presented a mean REGICOR risk score of 7.7% (4.4%) versus 4.5% (3.3%) in the group without evidence of AsP (Table 1). Consequently, the REGICOR risk function significantly associated with presence of AsP ( $P=.001$ ) with an area under the ROC curve of 0.75. Population-wide analysis by risk category shows 32.2% of patients with low REGICOR risk presented AsP, as did 65.7% of moderate-risk and 75.6% of high-risk patients; differences between the groups were statistically significant (Tables 1 and 2). In 95.5% of patients with noncalcified plaques (21/22), REGICOR risk levels were low or moderate. The REGICOR risk levels in patients with significant lesions varied: in 3/13 (23.1%) risk was low; in 6/13 (46.2%), moderate; and in 4/13 (30.8%), high-very high.

In the follow-up, 1.5% of patients had coronary events (1 sudden death due to infarction; 2 unstable angina, 1 of them with percutaneous treatment). All the patients who had events during follow-up, showed nonobstructive AsP in the NCA-MDCT, 1 of them without presence of coronary calcium, with low risk in 1 patient and moderate risk in the other 2.

Prevalence of silent AsP in our series was high (53%). Among the few publications on the topic, the largest study ( $n=4320$ ) showed 24% prevalence,<sup>4</sup> less than in our series, in a population that was younger, of Asiatic origin, with a higher proportion of women and lower prevalence of risk factors.

In our series, risk factors—except hypertension, body mass index and diabetes mellitus—associated significantly with AsP (Table 1). However, in the coronary risk analysis, 26% of patients with AsP had a low REGICOR risk score and just over 45% of affected