Journal of Cardiology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

Incidence of hospital-acquired hyponatremia by the dose and type of diuretics among patients with acute heart failure and its association with long-term outcomes

Masahiro Yamazoe (MD, PhD)[a], Atsushi Mizuno (MD)[b], Shun Kohsaka (MD, PhD)[c,*], Yasuyuki Shiraishi (MD, PhD)[c], Takashi Kohno (MD, PhD)[c], Ayumi Goda (MD, PhD)[d], Satoshi Higuchi (MD)[d], Mayuko Yagawa (MD)[e], Yuji Nagatomo (MD, PhD)[e], Tsutomu Yoshikawa (MD, PhD, FJCC)[e] for the West Tokyo Heart Failure Registry Investigators Tokyo, Japan

[a] Department of Bio-informational Pharmacology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan
[b] Department of Cardiology, St Luke's International Hospital, Tokyo, Japan
[c] Department of Cardiology, Keio University School of Medicine, Tokyo, Japan
[d] Division of Cardiology, Kyorin University School of Medicine, Tokyo, Japan
[e] Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan

ARTICLE INFO

Article history:
Received 14 July 2017
Received in revised form 21 September 2017
Accepted 25 September 2017
Available online xxx

Keywords:
Hyponatremia
Heart failure
Thiazide diuretics
Loop diuretics

ABSTRACT

Background: Diuretics are the cornerstone therapy for acute heart failure (AHF) but can lead to various electrolyte disturbances and inversely affect the patients' outcome. We aimed to evaluate whether (1) the dose of loop diuretics could predict hospital-acquired hyponatremia (HAH) during AHF treatment, (2) addition of thiazide diuretics could affect development of HAH, and (3) assess their impact on long-term outcomes.

Methods: We analyzed the subjects enrolled in the multicenter AHF registry (WET-HF). Risk of HAH, defined as hyponatremia at discharge with normonatremia upon admission, was evaluated based on oral non-potassium-sparing diuretics via multivariate logistic regression analysis. Additionally, we performed one-to-one matched analysis based on propensity scores for thiazide diuretics use and compared long-term mortality.

Results: Of total 1163 patients (mean age 72.6 ± 13.6 years, male 62.6%), 92 (7.9%) had HAH. Compared with low-dose loop diuretics users (<40 mg; without thiazide diuretics), risks for developing HAH were significantly higher in patients with thiazide diuretics, regardless of the dose of loop diuretics (OR 2.67, 95% CI 1.13–6.34 and OR 2.31, 95% CI 1.50–5.13 for low- and high-dose loop diuretics, respectively). The association was less apparent in patients without thiazide diuretics (OR 1.29, 95% CI 0.73–2.27 for high-dose loop diuretics alone). Among 206 matched patients, all-cause and cardiac mortality rate was 27% and 14% in non thiazide diuretics users and 50% and 30% in thiazide diuretics users, respectively (HR 2.46, 95% CI 1.29–4.69, $p = 0.006$ and HR 2.50, 95% CI 1.10–5.67, $p = 0.028$, respectively) during a mean 19.3 months of follow-up.

Conclusions: Thiazide diuretics use, rather than loop diuretics dose, was independently associated with HAH; and mortality was higher in thiazide diuretics users even after statistical matching.

Introduction

Acute decompensation of heart failure (AHF) is primarily caused by increased filling pressure of the left ventricle due to increased volume overload [1], and diuretics, in many forms, are

* Corresponding author at: Division of Cardiology, Department of Medicine, Keio University School of Medicine, 35 Shinanomachi Shinjuku-ku, Tokyo 160-8582, Japan.
E-mail address: kohsaka@cpnet.med.keio.ac.jp (S. Kohsaka).

https://doi.org/10.1016/j.jjcc.2017.09.015
0914-5087/

the cornerstone of its acute-phase treatment. However, its use has been shown to impair long-term mortality [2]. Patients administered high doses of diuretics [3–5] have been particularly noted to be at higher risk for adverse clinical events such as death or rehospitalization. Whether this relationship is causal or, using high-dose and multiple types of diuretics just represents a marker of more advanced disease, remains unclear.

Further, diuretics, at higher doses and simultaneous use of loop diuretics and thiazide and thiazide-type diuretics (TZ) are known to induce iatrogenic hyponatremia [6]. Hyponatremia defined as serum sodium (Na) concentration < 135 mEq/L is common in AHF, and has been documented to not only reflect AHF severity, but also be a strong predictor of adverse short- and long-term outcomes [7–9]. Reports have shown that hospital-acquired (progressive) hyponatremia, rather than hyponatremia based on single measurement at admission, was associated more strongly with an increased risk for adverse events, including prolonged hospital stay [10] and mortality [11]. However, the impact of diuretic management in the acute phase of AHF on hospital-acquired hyponatremia remains to be elucidated. Unfortunately, conducting sufficiently powered, prospective, randomized clinical trials to investigate the effect of diuretics types and dose on adverse outcomes in patients with AHF are challenging.

The purpose of this study was to assess the hypothesis that diuretic use, in its higher dose or additional use of TZ, is an independent predictor for hospital-acquired hyponatremia, and possibly for long-term adverse outcomes in patients with AHF. Quantification of their effects on sodium imbalance could aid physicians in the appropriate choice of the medications and dosing.

Methods

Study population

We retrospectively analyzed the data from 1844 consecutive AHF cases registered in the West Tokyo Heart Failure (WET-HF) registry from January 2006 to November 2015. This database is an ongoing, prospective, multicenter registry designed to collect the clinical background and outcome data of patients with AHF; patients presenting with AHF complicated with acute coronary syndrome were not included. The WET-HF registry recruited patients from four teaching hospitals within the metropolitan Tokyo area in Japan. Diagnosis of AHF was based on Framingham criteria [12]. Approximately 100 variables were collected from each patient. Participating hospitals were instructed to record and register data from consecutive hospital visits for AHF using an internet-based data collection system. The data entered were checked for completeness and internal consistency. Quality assurance was achieved through automatic system validation and reporting of data completeness and through education and

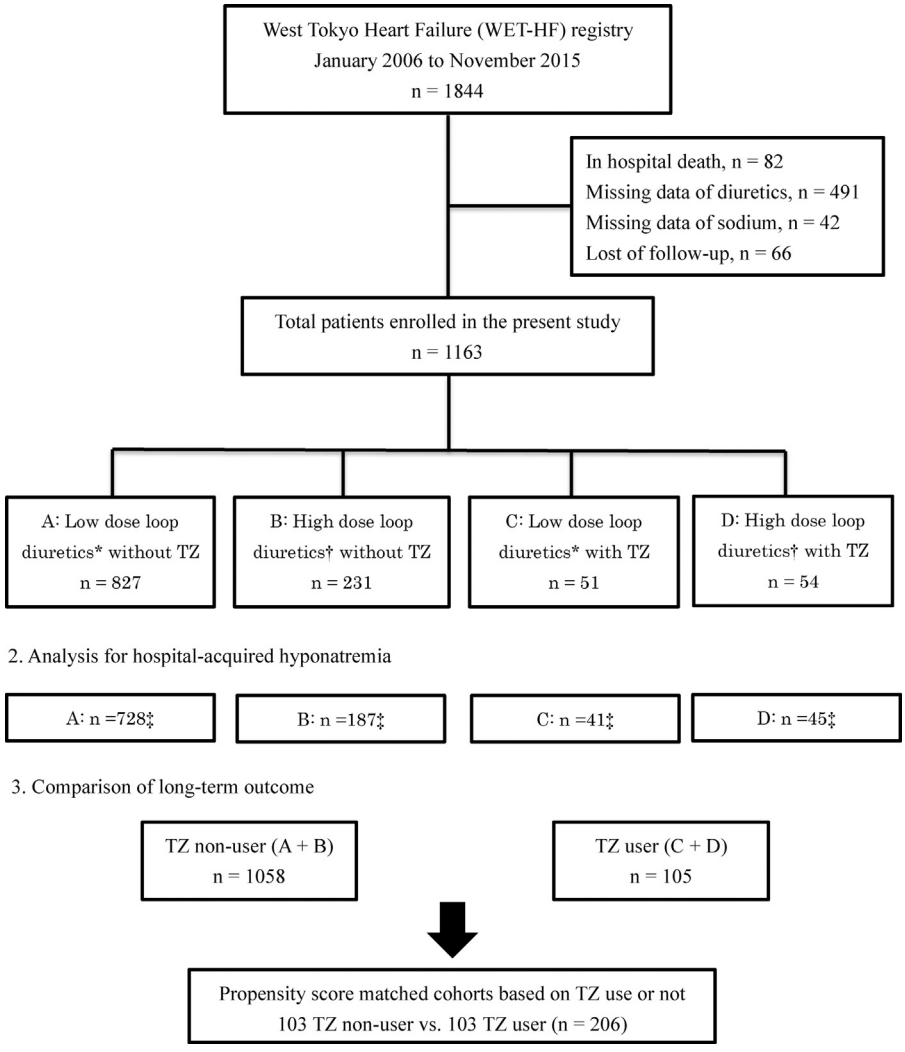

Fig. 1. Study flow chart. TZ, thiazide and thiazide-type diuretics. *, Dose of loop diuretics <40 mg, †, dose of loop diuretics ≥40 mg, ‡, number of patients with normonatremia at admission.

Please cite this article in press as: Yamazoe M, et al. Incidence of hospital-acquired hyponatremia by the dose and type of diuretics among patients with acute heart failure and its association with long-term outcomes. J Cardiol (2018), https://doi.org/10.1016/j.jjcc.2017.09.015