Journal of Cardiology 74 (2019) 195–196

Contents lists available at ScienceDirect

Journal of Cardiology

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

Letters to the Editor

Interpreting the evidence from tolvaptan clinical trials

We read with great interest the review article by Imamura and Kinugawa [1], entitled "Update of acute and long-term tolvaptan therapy," which gives a comprehensive overview of a diuretic treatment strategy for heart failure (HF). In Japan, tolvaptan has been approved for the treatment of patients with volume overload due to HF unresponsive to other conventional diuretic therapies, regardless of the serum sodium level. The use of tolvaptan for HF patients outside of Japan is rather infrequent and 'hypervolemic and euvolemic hyponatremias' are the main indication for its use in most Western countries.

In their review, Imamura and Kinugawa provide an excellent outline for both the short- and long-term uses of tolvaptan in HF patients. However, they discuss the relevant clinical trials largely without considering the level of evidence. The authors support the use of tolvaptan on the basis of clinical studies focused on its hemodynamic effects and of associated laboratory test results (e.g. renal function) [2]. For example, they emphasize that tolvaptan did reduce left-side and right-side filling pressures without affecting the cardiac index [3]. We believe that the reader would benefit from a discussion with greater attention to larger randomized clinical trials, such as the Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure Study (TACTICS) and the Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure (SECRET of CHF), neither of which has shown a significant difference in the primary clinical endpoint of dyspnea between tolvaptan and placebo [4,5].

The most recent Japanese clinical practice guidelines have also stated tolvaptan to be a "renal protective" diuretic and have strongly recommended its use (class IIa with evidence level A) [2]. Patient characteristics and the baseline HF therapy might vary between different geographic areas [6,7], which might yield guideline recommendations specific to the patient population in each region. However, we would like to emphasize that hemodynamic outcomes of small clinical trials should be interpreted with caution; of the variables related to hemodynamics, none, other than pulmonary capillary wedge pressure [8], has shown a significant association with clinical outcomes. For this reason, Western clinical practice guidelines have typically relied upon studies that have assessed clinical endpoints.

HF remains a major clinical and economic problem for health care worldwide, and, unfortunately, over the past decade no prospective, randomized clinical trial has shown a single medication to improve clinical outcomes in the acute phase. Further ongoing studies of tolvaptan (such as Assessment of Quality of Life During Long-Term Treatment of Tolvaptan in Refractory Heart Failure: AQUA-TLV) [9] may shed light on this issue, but until then, we believe that caution is needed for the use of tolvaptan for treating both acute and chronic HF.

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Received 24 February 2019
Available online 2 April 2019

https://doi.org/10.1016/j.jjcc.2019.02.018