ESC HEART FAILURE
ESC Heart Failure 2018; **5**: 649–650
Published online 25 March 2018 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12229

Diuretic dosing in heart failure: more data are needed

In the study by Okabe *et al*.[1] the oral dose of 40 mg of furosemide proved being a cut-off beyond which both all-cause and cardiovascular mortality were significantly higher. The above-mentioned value has been obtained using C-statistics from a total of 215 chronic heart failure (CHF) patients investigated through a median follow-up of 641 days. This interesting inference has been derived from a relatively small sample of CHF patients and may be therefore deemed as hypothesis generating. However, the study is confined to finding an association without affirming any causal value of it. In other words, in this observational study, it is not excluded that adverse prognosis profiles of higher doses (>40 mg/d) might depend on a greater severity of the baseline clinical picture (so-called confounding by indication). Indeed, furosemide at doses of >40 mg/d is effective in reducing congestion, relieving cardiac workload, and decreasing ventricular wall stress, thereby preventing the progression of cardiac chambers' dilatation. However, these favorable effects might fail in improving survival for the simultaneous occurrence of unfavorable repercussions on other organs and apparatuses. For example, a greater electrolyte loss (consisting of increased urinary excretion of Na^+, K^+, Ca^{++}, and Mg^{++}) related to doses of >40 mg furosemide/d might worsen ruinous vertebral osteoporosis,[2] a disease relatively common in the elderly patients with cardiac decompensation, which results in fragility fractures or subluxations at the level of the spine with related neurological lesions (e.g. aching pain, paraplegia, and tetraplegia) with significant adverse impact on the patient's life expectancy. In addition, relatively high oral doses may excessively stimulate the macula densa receptors in the kidneys with tubule-glomerular feedback, resulting in diuretic resistance.[3]

Subsequent adoption of sequential blockade of the nephron by means of thiazide addition might favor the occurrence of hyponatremia,[4] resulting in neurological disturbances, such as postural instability and falls with the potential for fatal outcomes such as traumatic lesions (especially endocranial hematomas). Vasopressin antagonists prevent hyponatremia without increasing adverse events.[5]

Interferences between the dosage of diuretics and further factors of conditions such as the combination of diuretics with low-dose dopamine infusion and its significant biological effects such as improved renal function profile and potassium homeostasis have been described in the DAD-HF trial.[6] We conclude that we need more solid data deciphering these intricate interactions in heart failure, which might ultimately translate to improved prognosis of this disease being associated with high mortality and morbidity.[7]

Conflict of interest

M.N. has received grants from the Deutsche Forschungsgemeinschaft (DFG) through the Sonderforschungsbereich Transregio 19 "Inflammatory Cardiomyopathy" (SFB TR19) (TP B2), and from the University Hospital Giessen and Marburg Foundation Grant "T cell functionality" (UKGM 10/2009). C.T. has received a grant from the DFG (SFB TR19 TP B5 and Z3). M.N. has been consultant to the IKDT (Institute for Cardiac Diagnosis and Therapy GmbH, Berlin) June 2004–June 2008 and has received honoraria for presentations and/or participated in advisory boards from AstraZeneca, Bayer, Fresenius, Miltenyi Biotech, Novartis, Pfizer, and Zoll. M.N. is among others the local p.i. of the RELAX-AHF-2 and TRANSITION trials at the site University Hospital Jena. The remaining authors, i.e. R.D.V., A.R., B.B., and A.M., declare that they have no conflict of interest.

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