**Manuscript Number:**  ESCHF-17-00134

**Full Title:**  Diuretic dosing in heart failure - more data are needed

**Article Type:**  Letter to the Editor

**Corresponding Author:**  Renato De Vecchis  
Cardiology Unit, Presidio Sanitario Intermedio  
Napoli, Campania ITALY

**Corresponding Author's Institution:**  Cardiology Unit, Presidio Sanitario Intermedio

**Corresponding Author's Secondary Institution:**

**Corresponding Author E-Mail:**  r.de.vecchis@alice.it

**First Author:**  Renato De Vecchis

**Order of Authors:**  
Renato De Vecchis  
Angelos Rigopoulos  
Boris Bigalke  
Athanassios Manginas  
Carsten Tschöpe  
Michel Noutsias

**Order of Authors Secondary Information:**

**Suggested Reviewers:**

**Author Comments:**
1 Letter to the Editor regarding ESCHF-17-00064:
2 Okabe T, Yakushiji T, Kido T, et al.: “The association between high-dose loop diuretic use at
discharge and cardiovascular mortality in patients with heart failure”; ESC Heart Fail 2017 (in
press)

3 Diuretic dosing in heart failure – more data are needed
4 Renato De Vecchis, MD¹, Angelos Rigopoulos, MD², Boris Bigalke, MD, MBA³,
5 Athanassios Manginas, MD⁴, Carsten Tschöpe, MD⁵.⁶.⁷, Michel Noutsias, MD²

6 1) Cardiology Unit, Presidio Sanitario Intermedio "Elena d'Aosta", via Cagnazzi 29, c.a.p. 80137
7 Napoli, Italy; devecchis.erre@virgilio.it
8 2) Department of Internal Medicine III, Division of Cardiology, Angiology and Intensive Medical
9 Care, University Hospital Halle, Martin-Luther-University Halle, Ernst-Grube-Straße 40, D-
10 06120 Halle (Saale), Germany; angelos.rigopoulos@gmail.com; Michel.Noutsias@gmx.de
11 3) Department of Cardiology, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin
12 (CBF), Berlin, Germany; boris.bigalke@charite.de
13 4) Interventional Cardiology and Cardiology Department, Mediterraneo Hospital, Ilias Street 8-12,
14 16675 Glyfada, Greece; nassoseft@yahoo.com
15 5) Department of Cardiology, Charité - Universitätsmedizin Berlin, Campus Virchow Klinikum
16 (CVK), Berlin, Germany; ctschoepe@yahoo.com
17 6) Deutsches Zentrum für Herz Kreislaufforschung (DZHK) – Standort Berlin, Charité -
18 Universitätsmedizin Berlin, Campus Virchow Klinikum (CVK), Berlin, Germany
19 7) Berlin Center for Regenerative Therapies (BCRT), Campus Virchow Klinikum (CVK), Berlin,
20 Germany

21 Corresponding author:
22 Dr. Renato De Vecchis
23 Cardiology Unit,
24 Presidio Sanitario Intermedio
25 "Elena d'Aosta"
26 Napoli
27 Italy
28 Phone: +393483313530
29 Fax: +390812543144 - 45
30 Email: devecchis.erre@virgilio.it; r.de.vecchis@alice.it
Keywords

heart failure; diuretics; prognosis
Letter to Editor:

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 >40mg/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, 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. 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.

Acknowledgements
None.

Potential Conflicts of interest:
MN has received grants by the Deutsche Forschungsgemeinschaft (DFG) through the Sonderforschungsbereich Transregio 19 “Inflammatory Cardiomyopathy” (SFB TR19) (TP B2), and by the University Hospital Giessen and Marburg Foundation Grant “T cell functionality” (UKGM 10/2009). CT has received a grant by the DFG (SFB TR19 TP B5 and Z3). MN has been consultant to the IKDT (Institute for Cardiac Diagnosis and Therapy GmbH, Berlin) 06/2004-06/2008, and has received honoraria for presentations and/or participated in advisory boards from AstraZeneca, Bayer, Fresenius, Miltenyi Biotech, Novartis, Pfizer and Zoll. MN 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., RDV, AR, BB and AM declare that they have no conflict of interest.

References:
4) De Vecchis R, Ariano C, Esposito C, Giasì A, Cioppa C, Cantatrione S. In right or biventricular chronic heart failure addition of thiazides to loop diuretics to achieve a sequential blockade of
the nephron is associated with increased risk of dilutional hyponatremia: results of a case-control study. Minerva Cardioangiol. 2012 Oct;60(5):517-29.

