# LETTERS TO THE EDITOR

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## Urinary sodium evaluation: the missing target for diuretic treatment optimization in acute heart failure patients? Letter regarding the article 'Clinical importance of urinary sodium excretion in acute heart failure'

We read with interest the paper by Damman *et al.*[1] describing the clinical importance of early urinary sodium (uNa) excretion in acute heart failure (AHF) patients. We fully agree with the potential interest of uNa monitoring in this context. The strength of uNa excretion could be its ability to combine, in a single parameter, urinary volume and spot sodium concentration, both target criteria suggested by the Heart Failure Association therapeutic algorithm of congestive AHF.[2] Moreover, it seems to perform even better as a prognostic predictor than these two indicators considered separately.

However, we have some comments on the paper. The observational design and the absence of a prospective protocol led to significant potential biases. For example, an appraisal of the congestion status at presentation is lacking: an objective evaluation (i.e. "wet score"[3]) may allow for a more genuine interpretation of the uNa-independent prognostic role. In fact, admitted patients, depending on their congestion grade and on doses and timing of intravenous diuretic administration in the emergency department, may be in a different position in the time-natriuresis curve. Another interesting point to be elucidated is whether uNa maintains its predictive role irrespective of baseline ejection fraction and the use of inotropes/vasopressors, which was not standardized.

Nevertheless, the way through which this parameter would affect mortality without a solid correlation with heart failure rehospitalizations remains unclear. It would therefore be interesting to evaluate the association of 6 h uNa excretion with other surrogated endpoints, such as the incidence of treatment failure, worsening renal function (WRF) or changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP). In a recent sub-analysis of the DRAIN randomized controlled trial, we demonstrated the association between low early uNa spot and worse diuretic response in patients admitted for acute decompensation of advanced chronic heart failure with a high risk of diuretic resistance.[4,5] Early spot uNa ≤50 mmol/L was associated with higher levels of NT-proBNP and a higher incidence of WRF at 72 h, suggesting worse unloading of these patients after a standardized therapeutic protocol.

In conclusion, even if we agree on the appealing idea of uNa as a single, low-cost and precocious indicator of AHF outcome, caution must be taken in the interpretation of this value, which needs to be contextualized in a global clinical assessment. Prospective randomized studies are needed to elucidate if natriuresis only represents a predictor of diuretic response and, eventually, a prognostic marker, or may be a therapeutic goal for unloading.

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### References

1. Damman K, Ter Maaten JM, Coster JE, Krikken JA, van Deursen VM, Krijnen HK, Hofman M, Nieuwland W, van Veldhuisen DJ, Voors AA, van der Meer P. Clinical importance of urinary sodium excretion in acute heart failure. *Eur J Heart Fail* 2020;**22**:1438–1447.
2. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WH, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.
3. Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JE, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJ, Filippatos G. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail* 2010;**12**:423–433.
4. Frea S, Pidello S, Volpe A, Canavosio FG, Galluzzo A, Bovolo V, Camarda A, Golzio PG, D'Ascenzo F, Bergerone S, Rinaldi M, Gaita F. Diuretic treatment in high-risk acute decompensation of advanced chronic heart failure – bolus intermittent vs. continuous infusion of furosemide: a randomized controlled trial. *Clin Res Cardiol* 2020;**109**:417–425.
5. Galluzzo A, Frea S, Boretto P, Pidello S, Volpe A, Canavosio FG, Golzio PG, Bergerone S, De Ferrari GM. Spot urinary sodium in acute decompensation of advanced heart failure and dilutional hyponatremia: insights from DRAIN trial. *Clin Res Cardiol* 2020;**109**:1251–1259.

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## Urinary sodium evaluation: the missing target for diuretic treatment optimization in acute heart failure patients? Reply

Dr Galluzzo *et al.* commented on our manuscript on urinary sodium content after diuretic initiation in acute heart failure (HF).[1] They expressed their concerns on the absence of a prospective protocol and the fact that there was no estimate of congestion (score) available. The Authors suggest that given these limitations, patients could have been presenting at different positions at the 'time-natriuresis' curve. Certainly, we acknowledge that the observational nature of our study is a limitation.[1] However, our findings are a reflection of 'real-world' data, which also inherently means that there was no structural scoring of congestion at start of treatment. It is also important to realize that our primary findings were based on 6 h urinary sodium content. Although many patients improve clinically during the first hours of treatment, it is not likely assessment of congestion at baseline would have altered our findings at 6 h. We did show that patients who had lower urinary sodium content at 6 h had evidence of more severe HF with higher natriuretic peptide levels at baseline, lower blood pressure, worse renal function, more frequent use of loop diuretics at baseline and more use of inotropes and vasopressors.

The Authors point to their subanalysis of the small DRAIN study in 80 patients, where they evaluated early (2 h) spot urinary sodium content and surrogate outcome measures and found similar results as compared with our analyses.[2] Our results should be interpreted slightly different, considering we evaluated total urinary sodium content over 6 h, which is probably a better representation of total natriuretic response to a given diuretic dose than spot urinary sodium.[3–5] With regard to the inotrope/vasopressor regimen not being standardized in our cohort, we consider these therapies only in very selected patients, according to the European Society of Cardiology HF guidelines, where they are only advocated in a small proportion of acute HF patients with severe hypotension.[6] In our study, the prognostic information of urinary sodium content at 6 h was unchanged by adjusting for inotrope/vasopressor use [hazard ratio (HR) 1.05, 95% confidence interval (CI) 1.01–1.08, $P = 0.008$, per 10 mmol decrease ($n = 146$)] or left ventricular ejection fraction [(HR 1.05, 95% CI 1.01–1.08, $P = 0.003$, per 10 mmol decrease ($n = 157$)]. Change in natriuretic peptide level was only available in a subset of patients at 24 h after admission, and was not different in tertiles of urinary sodium ($P = 0.69$ and $P = 0.67$ for absolute and relative change, respectively).

We do not think worsening renal function (WRF), as used by the Authors, is an appropriate surrogate endpoint in acute HF patients without considering natriuretic/diuretic response. WRF in a patient with good natriuresis is not true WRF and should be termed pseudo-WRF, and cannot directly be compared with WRF in patients with poor natriuresis/diuretic response, according to most recent position papers on how to evaluate renal function in HF.[7,8] For instance, in our cohort and using different definitions, WRF was consistently more frequent in patients with the highest urinary sodium content at 6 h. Yet, the prognostic information of urinary sodium at 6 h was unaffected by the occurrence of WRF, and WRF itself was not independently associated with clinical outcome. This again highlights not to use serum creatinine/WRF as a response marker during decongestion in acute HF.

Finally, the finding that urinary sodium content at 6 h was only associated with all-cause mortality and appeared not to be associated with HF readmission is probably related to the severity of HF in our tertiary HF clinic, as well as a tendency of some elderly patients with HF at our clinic to decide not to be readmitted after discharge as part of advanced care planning. Therefore, we also evaluated the combined endpoint of mortality and HF rehospitalization, confirming our primary results. We agree with the Authors that we need prospective randomized studies to evaluate whether this cheap and easy marker of natriuretic/diuretic response is a valuable tool to assess treatment effect or can serve as therapeutic target in a cute HF.

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## References

1. Damman K, Ter Maaten JM, Coster JE, Krikken JA, van Deursen VM, Krijnen HK, Hofman M, Nieuwland W, van Veldhuisen DJ, Voors AA, van der Meer P. Clinical importance of urinary sodium excretion in acute heart failure. *Eur J Heart Fail* 2020;**22**:1438–1447.
2. Galluzzo A, Frea S, Boretto P, Pidello S, Volpe A, Canavosio FG, Golzio PG, Bergerone S, De Ferrari GM. Spot urinary sodium in acute decompensation of advanced heart failure and dilutional hyponatremia: insights from DRAIN trial. *Clin Res Cardiol* 2020;**109**:1251–1259.
3. Singh D, Shrestha K, Testani JM, Verbrugge FH, Dupont M, Mullens W, Tang WH. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompensated heart failure. *J Card Fail* 2014;**20**:392–399.
4. Honda S, Nagai T, Nishimura K, Nakai M, Honda Y, Nakano H, Iwakami N, Sugano Y, Asaumi Y, Aiba T, Noguchi T, Kusano K, Yokoyama H, Ogawa H, Yasuda S, Anzai T; NaDEF Investigators. Long-term prognostic significance of urinary sodium concentration in patients with acute heart failure. *Int J Cardiol* 2018;**254**:189–194.
5. Biegus J, Zymlinski R, Sokolski M, Todd J, Cotter G, Metra M, Jankowska EA, Banasiak W, Ponikowski P. Serial assessment of spot urine sodium predicts effectiveness of decongestion and outcome in patients with acute heart failure. *Eur J Heart Fail* 2019;**21**:624–633.
6. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
7. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, Tang WHW, Skouri H, Verbrugge FH, Orso F, Hill L, Dilek U, Lainscak M, Rossignol P, Metra M, Mebazaa A, Seferovic P, Ruschitzka F, Coats A. Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:584–603.
8. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WH, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.

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# Effects of vericiguat in heart failure with reduced ejection fraction: do not forget sST2. Letter regarding the article 'Baseline features of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial'

We read with interest the paper by Pieske *et al.*[1] describing the baseline characteristics of patients enrolled in the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial. Despite the quite extensive description of patient characteristics at baseline, no information about heart failure (HF) biomarkers other than natriuretic peptides is available. Specifically, data about high-sensitivity cardiac troponin T (hs-cTnT) and soluble suppression of tumorigenesis-2 (sST2) have not been provided, although these biomarkers yield strong and independent prognostic significance beyond natriuretic peptides for the prediction of all-cause and cardiovascular mortality and HF hospitalization in patients with chronic HF, particularly those with HF and reduced ejection fraction (HFrEF). While hs-cTnT will be analysed in a planned *post-hoc* analysis of the VICTORIA trial, sST2 apparently will not.[2] This attitude of study investigators may be related to the results of the SOCRATES-PRESERVED (Soluble Guanylate Cyclase Stimulator in Heart Failure Patients with Preserved Ejection Fraction) trial, where no change in sST2 levels was observed, although this was in line with the overall trend of other cardiac biomarkers in this study population, including natriuretic peptides.[3] Conversely, sST2 was not evaluated in the SOCRATES-REDUCED (Soluble