



Prevalence and outcome of diuretic resistance in heart failure: reply

Joan-Carles Trullàs^{1,2} · Jesús Casado³ · Jose-Luís Morales-Rull⁴ · Francesc Formiga⁵ · Luis Manzano⁶

Received: 21 February 2019 / Accepted: 26 February 2019 / Published online: 6 March 2019
© Società Italiana di Medicina Interna (SIMI) 2019

Dear Sir,

First of all we would like to thank Dr. Carrizales-Sepulveda and his collaborators for their interest and comments in our work [1]. We completely agree that diuretic resistance is a complex situation, with multiple etiologies and in some cases multifactorial. It would be desirable to identify the main cause that contributes to diuretic resistance in every single case and focus on its treatment to enhance diuretic response. This theoretical approach is sometimes difficult to perform in clinical practice.

We have also read with great interest the position paper about the practical use of diuretics in patients with acute and chronic heart failure (HF) [2]. Surprisingly, there is still little evidence about the use of diuretics in HF and the majority of the recommendations about their use are based on expert opinion. The proposed flowchart for a stepped approach will be useful to early detect unresponsive patients by measuring urinary sodium and urinary output after an initial dose of intravenous diuretics.

In our experience, more than half of the patients admitted for HF decompensation are already receiving chronic loop diuretic treatment and up to 21% in doses equal to or greater than 80 mg per day of oral furosemide [3]. It is very likely

that many of these patients have “true” diuretic resistance because prolonged exposure to loop diuretics causes renal adaptation, with progressive hypertrophy and hyperfunction of the distal nephron, increasing local sodium reabsorption. This effect markedly limits the response to loop diuretics. In our opinion, this clinical scenario (hospitalization for chronic HF decompensation despite receiving high dose of oral furosemide), could be an earlier indicator of poor response to intravenous diuretic treatment.

As recommended in the aforementioned algorithm [2], we agree to use thiazide-type diuretic as first line of combined diuretic treatment when there is resistance to loop diuretics. However, the question is when is the most appropriate time to add a thiazide-type diuretics? Do we have to wait until the loop diuretic doses are maximal (as suggested in the flowchart) or could we start earlier? Our opinion is that early addition of a thiazide-type diuretic can be an effective and faster strategy to improve congestion, especially in loop diuretics non-naïve patients. To prove this hypothesis, we are carrying out a multicenter, double-blind, phase IV clinical trial (CLOROTIC, NCT01647932) to determine whether the addition of a thiazide-type diuretic (hydrochlorothiazide) to an intravenous loop diuretic treatment is superior to placebo in improving congestive symptoms in patients admitted for acute HF. The design of the study has been explained in detail elsewhere [4]. At the current moment, the study is in the final phase of recruitment and we hope to communicate the preliminary results in this year.

HF is a syndrome of epidemic proportions for which we use diuretic treatment very frequently. In spite of this, the scientific evidence about how we should use diuretics is too scarce and even more when resistance appears. It is necessary and mandatory to perform more research to better understand the pathophysiology and therapeutic approach of diuretic resistance.

✉ Joan-Carles Trullàs
jctv5153@comg.cat

¹ Internal Medicine Service, Hospital de Olot, Av. Dels Països Catalans, 86, 17800 Olot, Girona, Spain

² Medical Sciences Department, Universitat de Girona, Girona, Spain

³ Internal Medicine Service, Hospital Universitario de Getafe, Madrid, Spain

⁴ Internal Medicine Service, Hospital Universitario “Arnau de Vilanova”, IRBLleida, Lleida, Spain

⁵ Internal Medicine Service, Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Barcelona, Spain

⁶ Internal Medicine Service, Hospital Universitario Ramón Y Cajal, Universidad de Alcalá (IRYCIS), Madrid, Spain

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights The RICA registry complies with the Declaration of Helsinki. The local ethics committee from the University Hospital “Reina Sofia” (Córdoba, Spain) approved the study protocols.

Informed consent Informed consent was obtained from all participating subjects.

References

1. Carrizales-Sepúlveda EF, Vera-Pineda R, Jiménez-Castillo RA, Benavides-González MA, Ordaz-Farías A. Prevalence and outcome of diuretic resistance in heart failure: comment (2019) *Intern Emerg Med*. <https://doi.org/10.1007/s11739-019-02050-2>
2. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ (2019) 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* 21:137–155
3. Trullàs JC, Casado J, Morales-Rull JL, Formiga F, Conde-Martel A, Quirós R, Epelde F, González-Franco A, Manzano L, Montero-Pérez-Barquero M (2019) Prevalence and outcome of diuretic resistance in heart failure. *Intern Emerg Med*. <https://doi.org/10.1007/s11739-018-02019-7>
4. Trullàs JC, Morales-Rull JL, Casado J, Freitas Ramírez A, Manzano L, Formiga F (2016) Rationale and design of the “Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC Trial”): a double-blind, randomized, placebo-controlled study to determine the effect of combined diuretic therapy (loop diuretics with thiazide-type diuretics) among patients with decompensated heart failure. *J Card Fail* 22:529–536

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.