Revista Portuguesa de Cardiologia 43 (2024) 523–524

Portuguese Society of CARDIOLOGY

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Exploring the evidence gap: Loop diuretic withdrawal in chronic heart failure

Gap na evidência: Suspensão de diuréticos na insuficiência cardíaca crónica

Aurora Andrade

Clínica de Insuficiência Cardíaca, Serviço de Cardiologia, Unidade Local de Saúde Tâmega e Sousa, Penafiel, Portugal

Available online 27 July 2024

Significant advancements have been made in the treatment of chronic heart failure (HF) with reduced ejection fraction (HFrEF) in recent decades. The role of pharmacotherapy in changing disease progression has never been more crucial. The primary pharmacological treatments for HFrEF include angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor/neprilysin inhibitors (ARNIs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2is), all supported by strong evidence from randomized clinical trials (RCTs).[1]

Despite these advances and regardless of the individual course of each patient, HF remains a chronic condition with a fluctuating trajectory. Episodes of decompensation, mainly characterized by pulmonary or peripheral congestion, are common, require treatment adjustments, and are a major cause of symptoms, poor quality of life and adverse outcomes.[2] Loop diuretics are critical for the management of congestion, but once euvolemia is achieved, dose reduction or discontinuation is recommended.[1] However, there is limited information on the effects of discontinuing loop diuretics in euvolemic patients.[3] Continuous use in these patients may lead to further neurohormonal activation, electrolyte imbalance, renal dysfunction and symptomatic hypotension, potentially affecting the use of prognosis-modifying drugs.[4,5]

Historically, the management of diuretics in chronic HF patients has been inconsistent. The majority of ambulatory patients with chronic HFrEF are under diuretic therapy,[6] but there is little consensus on the long-term goals.[3] The impact of diuretics on disease progression and survival is unclear, with a lack of large-scale prospective RCTs to support their chronic use.

A retrospective analysis by Damman et al. suggested an association between the use of loop diuretics, higher loop diuretic dose and risk of adverse clinical outcomes, particularly HF hospitalizations.[7] Although an extensive and detailed statistical analysis was carried out, this type of data is prone to bias, as sicker patients tend to receive higher diuretic doses. A meta-analysis by Faris et al. suggested that diuretics might reduce the risk of death and worsening HF while improving exercise capacity. However, these data come from small and heterogeneous studies.[8]

Several questions arise regarding the ongoing use of diuretics in contemporary HFrEF treatment. Notably, the benefits of maintaining diuretic therapy are uncertain, especially as drugs like ARNIs, MRAs, and SGLT2is have shown mild diuretic effects or reduce the need for loop diuretics.[1] Furthermore, determining the appropriate method for assessing

E-mail address: amvandrade@hotmail.com

https://doi.org/10.1016/j.repc.2024.07.005

euvolemia and the suitability of diuretic withdrawal for all euvolemic patients remains challenging.

Limited data support the discontinuation of diuretic therapy in stable, euvolemic HFrEF patients. A study by Martens et al. demonstrated that down-titration of loop diuretics was feasible in a majority of 50 stable chronic HF patients over 30 days. Importantly, routine assessment with physical examination, transthoracic echocardiography and laboratory testing could not predict the success of down-titration.[9]

The study by Silva et al. published in this issue of the *Journal*[10] is noteworthy in addressing this pertinent topic. In a retrospective analysis, they assess the prognostic impact of diuretic therapy discontinuation in euvolemic HFrEF outpatients, using semiology to assess euvolemia. Among 129 HFrEF patients who at some point discontinued loop diuretics, only 14.8% experienced a congestive event within one year; 15 of these patients (83.3%) needed simple diuretic reinitiation at a scheduled visit, with a low loop diuretic dose. True worsening HF events occurred in only three patients (2.5%).

Applying these findings to the general HFrEF population is probably not straightforward. The study involved patients from a specialized HF clinic with extensive experience. Patients with severe symptoms (New York Heart Association [NYHA] class IV) or recent hospitalizations were excluded, ensuring stability but limiting generalizability. At baseline (first available appointment in the electronic medical record at which the patient was prescribed loop diuretics) the median age was 57.0 years, 95.8% of patients were in NYHA class I–II, median B-type natriuretic peptide level was 81.7 pg/ml, and median estimated glomerular filtration rate was 95.0 ml/min/1.73 m^2. Another important point is that only 25 patients (19.5%) presented signs of congestion and a low dose of furosemide was prescribed at baseline, with a median dose of 40 mg per day. Patients were well treated in terms of guideline-directed medical therapy, with optimization of prognosis-modifying drugs throughout follow-up. At loop diuretic withdrawal, 98.4% of patients were on ACEis/ARAs/ARNIs, 93.8% on BBs, 79.1% on MRAs and 22.5% on SGLT2is. It is important to note that most of the data were collected before the publication of the first trial showing the benefits of SGLT2is in HFrEF patients. Additionally, the median dose of furosemide at withdrawal was low (20 mg per day).

The investigators conclude that discontinuing loop diuretics in stable, euvolemic outpatients is associated with a low number of episodes of diuretic reintroduction and worsening HF events, and argue that discontinuation is possible in selected patients and certain conditions. As in other HFrEF treatments, patient phenotyping appears essential for optimal management.

Nevertheless, prospective randomized studies are warranted to determine whether systematic reduction of furosemide doses, or even discontinuation, in euvolemic HF patients can lead to improved clinical outcomes.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599–726.
2. Pellicori P, Cleland JG, Zhang J, et al. Cardiac dysfunction, congestion and loop diuretics: their relationship to prognosis in heart failure. Cardiovasc Drugs Ther. 2016;30:599–609.
3. Mullens W, Damman K, Harjola VP, et al. 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;21:137–55.
4. Martens P, Verbrugge FH, Nijst P, et al. Changes in loop diuretic dose and outcome after cardiac resynchronization therapy in patients with heart failure and reduced left ventricular ejection fractions. Am J Cardiol. 2017;120:267–73.
5. Maggioni AP, Dahlstrom U, Filippatos G, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013;15:808–17.
6. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail. 2017;19:1574–85.
7. Damman K, Kjekshus J, Wikstrand J, et al. Loop diuretics, renal function and clinical outcome in patients with heart failure and reduced ejection fraction. Eur J Heart Fail. 2016;18:328–36.
8. Faris RF, Flather M, Purcell H, et al. Diuretics for heart failure. Cochrane Database Syst Rev. 2012;2:CD003838.
9. Martens P, Verbrugge FH, Boonen L, et al. Value of routine investigations to predict loop diuretic down-titration success in stable heart failure. Int J Cardiol. 2018;250:171–5.
10. Silva G, Moura B, Moreira E, et al. Loop diuretic discontinuation in chronic heart failure patients: a retrospective study. Rev Port Cardiol. 2024;43:513–22.