



HAL
open science

Beyond loop diuretics: Unlocking the potential of co-diuretics in heart failure management

Nicolas Girerd

► **To cite this version:**

Nicolas Girerd. Beyond loop diuretics: Unlocking the potential of co-diuretics in heart failure management. *European Journal of Heart Failure*, 2023, 25 (8), pp.1334-1336. 10.1002/ejhf.2936 . hal-04142565

HAL Id: hal-04142565

<https://hal.univ-lorraine.fr/hal-04142565v1>

Submitted on 28 Jun 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Beyond Loop Diuretics:

Unlocking the Potential of Codiuretics in Heart Failure Management

Nicolas Girerd MD, PhD

Université de Lorraine, INSERM, Centre d'Investigations Cliniques 1433, CHRU de Nancy, Inserm 1116 and INI-CRCT (Cardiovascular and Renal Clinical Trialists) F-CRIN Network, Nancy, France;

Congestion, characterized by the accumulation of salt and water, lies at the heart of heart failure (HF), driving debilitating symptoms such as dyspnea and hospitalization. Loop diuretics have long been the primary therapeutic agents for addressing fluid overload, with dialysis as the only alternative for congestion removal. However, the optimal management of patients on loop diuretics remains a subject of debate. Despite numerous randomized trials conducted over the past three decades, no significant differences have been observed when comparing different loop diuretic strategies. One prominent example is the DOSE trial (1), which found no substantial distinction between repeated intravenous bolus and continuous infusions of furosemide. Recently, new approaches, including subcutaneous (SC) injections, have emerged for loop diuretic administration.

In this month's issue, Biegus and colleagues present a mechanistic study that adds valuable insights to our understanding of loop diuretics' effects (2). The study included fifty patients admitted within 36 hours of acute HF, comprising 28 furosemide-naïve individuals and 22 chronic furosemide users. The authors meticulously examined the association between previous furosemide use, diuretic response, and urine furosemide concentrations. Through this well-phenotyped cohort, the researchers standardized diuretic doses based on body weight and made notable observations. They found that chronic furosemide users exhibited urine furosemide excretion that was 30% lower compared to naïve patients (16.51 vs. 11.81 mg/6h, $p=0.01$). However, when accounting for estimated glomerular filtration rate (eGFR), a major determinant of excretion, furosemide excretion was similar across the groups (28.02 vs. 29.70 mg/6h, $p=0.87$). In contrast, the tubular response to administered loop diuretics was significantly higher in naïve patients compared to chronic users. Naïve patients exhibited

three times higher urine volume per 1 μ g/ml of urine furosemide at 2 hours (148.6 \pm 136.1 ml vs. 50.6 \pm 56.1 ml, p=0.005).

These findings significantly contribute to our understanding of the effects of loop diuretics. In patients with HF, particularly in the presence of significant congestion, the prevailing belief has been that insufficient tubular delivery hampers the effectiveness of loop diuretics due to absorption issues and reduced renal excretion. Decreased renal blood flow, impacting tubular delivery, has been suggested as a contributing factor (3). Moreover, the lower number or efficacy of furosemide transporters, such as Organic Anion Transporter-1 or 2, in chronic loop diuretic users may further limit tubular delivery. The common approach to address significant congestion involves switching to high-dose intravenous or SC infusions of furosemide to increase tubular concentration. However, the study by Biegus and colleagues challenges this strategy, revealing that it is the reduced tubular responsiveness to loop diuretics, rather than inadequate tubular delivery, that plays a significant role. Dose-response curves reported by the authors clearly demonstrate that increasing loop diuretic doses reach a plateau in terms of urine volume and sodium excretion, indicating that higher doses cannot compensate for the diminished responsiveness. Moreover, high-dose loop diuretics pose the risk of direct adverse effects, such as ototoxicity, which are concentration-dependent. Thus, relying solely on increased furosemide doses cannot resolve the issue.

The concept of blunted tubular response to loop diuretics and tubular remodeling

Biegus and colleagues' study breathes new life into the pathophysiological studies described almost four decades ago by Kaissling et al.(4). In their seminal paper, Kaissling et al. revealed significant hypertrophy of the distal convoluted tubule, resulting in tubular remodeling that impairs the response to loop diuretics by affecting Na⁺ tubular transporters. This morphological alteration forms the basis for the lack of diuretic efficacy observed in patients chronically treated with loop diuretics.

Can tubular remodeling be prevented?

Minimizing the long-term dose of diuretics appears to be a logical approach to mitigate tubular remodeling. This approach holds several practical advantages, particularly when encountering challenges associated with declining renal function (5) and low blood pressure (6), and when initiating HF drugs (7). However, the actual impact of long-term diuretic minimization has yet to be evaluated. The effectiveness of such an approach should be prospectively tested in clinical trials.

Codiuretics as the key to success?

Given that blunted responsiveness to loop diuretics appears to be the primary issue, it is imperative to explore strategies that enhance responsiveness. While minimizing chronic loop diuretic use serves as a preventive measure, when confronted with a patient experiencing acute HF and unresponsiveness to loop diuretics, the most pragmatic approach may involve employing codiuretics. Codiuretics, which possess diuretic effects distinct from loop diuretics but can enhance overall diuretic response, have traditionally been regarded as last-resort options. Promising candidates include high-dose mineralocorticoid receptor antagonists (MRA), thiazides, and more recently, acetazolamide. Limited evidence suggests the diuretic effects of MRAs. In an open-label trial, spironolactone increased natriuresis in patients hospitalized for acute HF (8). Some indications of efficacy have been observed with intravenous forms of MRAs, such as canrenoate potassium, in loop diuretic-refractory patients (9). Additionally, the safety profile of relatively high-dose intravenous MRAs appears favorable (10). Regarding thiazide use, the CLOROTIC trials recently demonstrated that hydrochlorothiazide led to significant weight loss, diuresis, and weight reduction compared to placebo at 72 and 96 hours. However, hydrochlorothiazide was associated with a higher incidence of impaired renal function, while rates of hypokalemia were similar between groups (11). Finally, the ADVOR trial revealed that acetazolamide exhibited superior efficacy in achieving successful decongestion compared to placebo, maintaining excellent safety with comparable rates of adverse events, worsening kidney function, hypokalemia, and hypotension between the groups (12). Although evidence exists for the acute efficacy of codiuretics, their use in chronic settings remains largely unexplored. It remains unknown whether utilizing codiuretics to reduce loop diuretic doses may result in less long-term tubular remodeling and preserved tubular response.

Advancing our understanding

Diuretics form the cornerstone of congestion management in HF, yet surprisingly few trials have been conducted to determine the optimal diuretic strategy. The recently published ADVOR and CLOROTIC trials offer refreshing insights into diuretic utilization. However, relying solely on isolated trials of moderate size may not provide all the answers. Larger confirmatory trials conducted in different geographical regions would be valuable. Moreover, many questions remain unanswered. Some of these questions include:

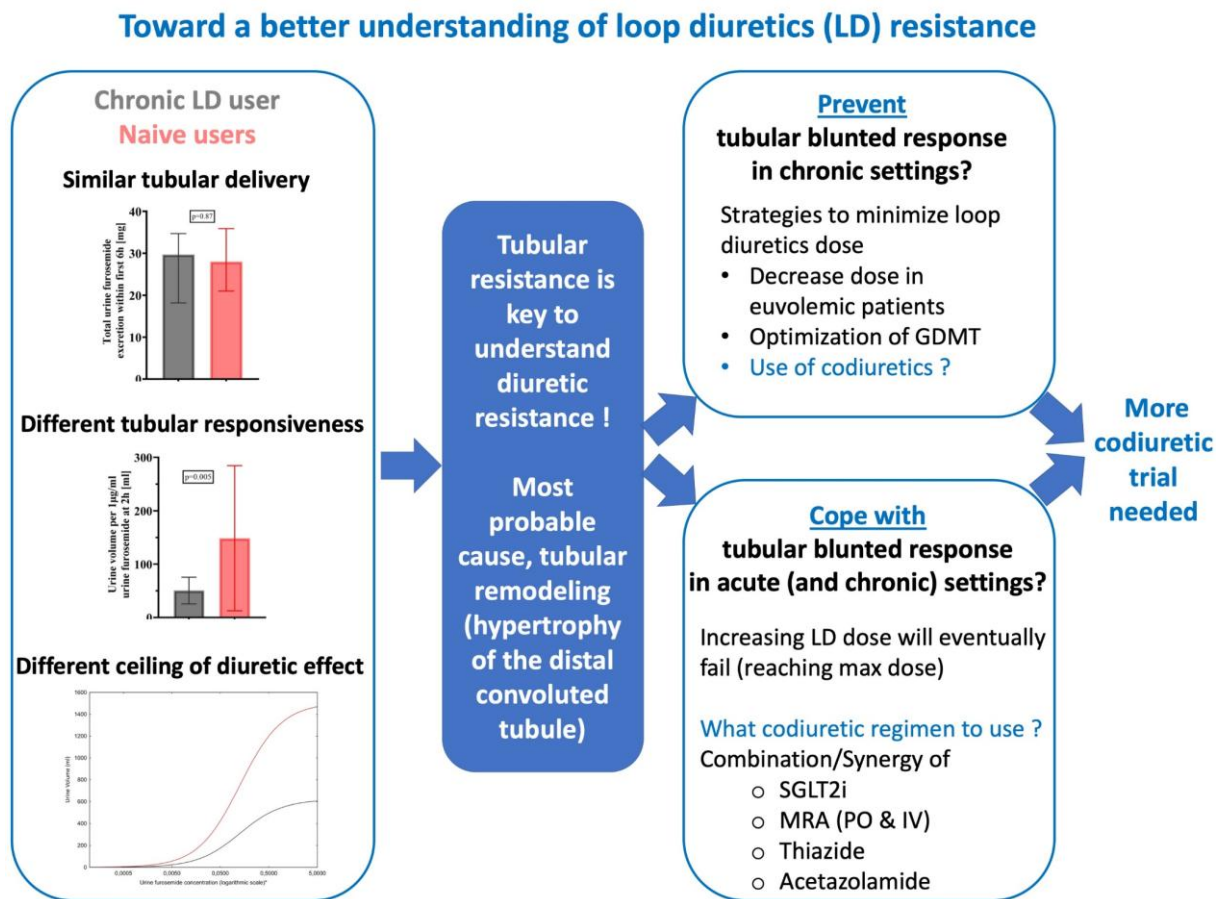
- a) The synergistic effects and safety of combined thiazide/acetazolamide use in acute settings.
- b) The synergistic effects and safety of thiazides or acetazolamide in patients concurrently treated with SGLT2 inhibitors in acute settings.
- c) The role of acetazolamide and thiazides in chronic/ambulatory settings.
- d) The role of canrenoate in acute settings.
- e) The impact of long-term co-diuretic use to reduce loop diuretic doses on long-term loop diuretic responsiveness.

Addressing these numerous questions could serve as the foundation for equally numerous clinical trials (Figure).

Another approach to advancing our understanding may lie in field experience. The Heart Failure Association has recently advocated for a more systematic approach to quantifying natriuresis (13). The use of natriuresis measurements is likely to enhance our comprehension of diuretic response, particularly when diuresis assessment alone is challenging. This approach could provide valuable field and clinical experience to address some of the aforementioned questions. However, despite its endorsement by the HFA, systematic implementation of this approach remains limited.

The future promises exciting discoveries as many aspects of diuretic therapy in HF remain to be unraveled. Let us hope that within the next few years, we will decipher the optimal utilization of diuretics, the age-old and fundamental treatment for HF.

Figure: Consequences of the key role of blunted tubular responsiveness to loop diuretics in diuretic resistance.



Bibliography

1. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011;364(9):797-805.
2. Biegus J, Zymlinski R, Testani J, Fudim M, Cox ZL, Guzik M, et al. The blunted loop diuretic response in acute heart failure is driven by reduced tubular responsiveness rather

than insufficient tubular delivery. The role of furosemide urine excretion on diuretic and natriuretic response in acute heart failure. *Eur J Heart Fail.* 2023.

3. Ellison DH, Felker GM. Diuretic Treatment in Heart Failure. *N Engl J Med.* 2017;377(20):1964-75.

4. Kaissling B, Bachmann S, Kriz W. Structural adaptation of the distal convoluted tubule to prolonged furosemide treatment. *Am J Physiol.* 1985;248(3 Pt 2):F374-81.

5. Mewton N, Girerd N, Boffa JJ, Courivaud C, Isnard R, Juillard L, et al. Practical management of worsening renal function in outpatients with heart failure and reduced ejection fraction: Statement from a panel of multidisciplinary experts and the Heart Failure Working Group of the French Society of Cardiology. *Arch Cardiovasc Dis.* 2020;113(10):660-70.

6. Cautela J, Tartiere JM, Cohen-Solal A, Bellemain-Appaix A, Theron A, Tibi T, et al. Management of low blood pressure in ambulatory heart failure with reduced ejection fraction patients. *Eur J Heart Fail.* 2020;22(8):1357-65.

7. Girerd N, Leclercq C, Hanon O, Bayes-Genis A, Januzzi JL, Damy T, et al. Optimisation of treatments for heart failure with reduced ejection fraction in routine practice: a position statement from a panel of experts. *Rev Esp Cardiol (Engl Ed).* 2023.

8. Ferreira JP, Girerd N, Medeiros PB, Santos M, Carvalho HC, Bettencourt P, et al. Spot urine sodium excretion as prognostic marker in acutely decompensated heart failure: the spironolactone effect. *Clin Res Cardiol.* 2016;105(6):489-507.

9. Girerd N, Aubry M, Lantelme P, Huttin O, Rossignol P. Intravenous Mineralocorticoid Receptor Antagonist Use in Acutely Decompensated Heart Failure with Diuretic Resistance. *Int Heart J.* 2021;62(1):193-6.

10. Berger C, Prieur C, Bochaton T, Berthiller J, Luyt CE, Bonnefoy-Cudraz E. Patients with acute heart failure treated with the CARRESS-HF diuretic protocol in association with canrenoate potassium: Tolerance of high doses of canrenoate potassium. *Arch Cardiovasc Dis.* 2020;113(11):679-89.
11. Trulls JC, Morales-Rull JL, Casado J, Carrera-Izquierdo M, Snchez-Marteles M, Conde-Martel A, et al. Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial. *Eur Heart J.* 2023;44(5):411-21.
12. Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *N Engl J Med.* 2022;387(13):1185-95.
13. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, 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(2):137-55.