Angiotensin Receptor Neprilysin Inhibitors in HFrEF: Is This the First Disease Modifying Therapy Drug Class Leading to a Substantial Reduction in Diuretic Need?

Brian Kerr, MB, BCh, MRCPI, Rebabonye B Pharithi, MB, BCh, MSc, MRCPI, Matthew Barrett, MB, BCh, MRCPI, Carmel Halley, MB, BCh, MD, Joe Gallagher, MD, Mark Ledwidge, PhD, and Kenneth McDonald, FESC, MD

1St. Vincent's University Hospital, Dublin, Ireland
2School of Medicine, University College Dublin, Dublin, Ireland

ABSTRACT

Despite significant advances in disease modifying therapy in heart failure (HF), diuretics have remained the cornerstone of volume management in all HF phenotypes. Diuretics, alongside their definite acute haemodynamic and symptomatic benefits, also possess many possible deleterious side effects. Moreover, questions remain regarding the prognostic impact of chronic diuretic use. To date, few data exist pertaining to diuretic reduction as a result of individual traditional guideline directed medical therapy in HF with reduced ejection fraction (HFrEF). However, diuretic reduction has been demonstrated with sacubitril/valsartan (angiotensin receptor-neprilysin inhibitor [ARNi]) from the PARADIGM study, as well as, post-marketing reports from our own group and others. Whether the ARNi compound represents the dawn of a new era, where effective therapies will have a more noticeable reduction on diuretic need, remains to be seen. The emergence of sodium glucose transport 2 inhibitors and guanylate cyclase stimulators may further exemplify this issue and potentially extend this benefit to HF patients outside of the HFrEF phenotype. In conclusion, emerging new therapies in HFrEF could reduce the reliance on diuretics in the management of this phenotype of HF. These developments further highlight the clinical importance to continually assess an individual’s diuretic requirements through careful volume assessment.

Keywords: Diuretics; Heart failure; Systolic heart failure; Angiotensin receptor antagonists; Neprilysin

INTRODUCTION

There have been significant advances in the management of heart failure with reduced ejection fraction (HFrEF) over the last several decades. Pharmacotherapy and device-based therapies have improved the quality of life and longevity of patients with this phenotype of heart failure (HF). However, despite these advances, there remains a dependency on diuretics, particularly loop diuretics, to maintain euvoolemia. While effective in this regard,
their use has the potential to adversely affect long term outcomes.\textsuperscript{1} This observation identifies a challenge for novel therapies, as efforts are made to further improve prognosis and symptoms in all HF phenotypes.

**EFFECTIVENESS AND DRAWBACKS OF DIURETIC THERAPY**

The effectiveness of diuretic therapy in managing hypervolemia is well-established. Loop diuretics in particular are the mainstay of therapy for symptom relief in 90% of patients presenting with acute decompensation.\textsuperscript{2} They also continue to be used in the vast majority of patients in the outpatient setting.\textsuperscript{2} The use of diuretics in the acute setting results in improvement of symptoms and haemodynamic measures, through natriuresis and prostaglandin mediated systemic venodilation.\textsuperscript{3}

However, downsides of this therapy are also well recognised. Both, thiazide and loop diuretics expose patients to a range of adverse endocrine, metabolic and electrolyte derangements.\textsuperscript{6} They also activate the renin-angiotensin-aldosterone system (RAAS), and excess use can lead to hypovolaemia. The latter could potentially worsen renal function and impede up-titration of guideline directed medical therapy (GDMT).\textsuperscript{5} However, Kapelios et al.\textsuperscript{6} failed to observe a loop diuretic dose increase hindering GDMT up-titration. Loop diuretics have been shown to elevate serum aldosterone and alter calcium handling in human subjects.\textsuperscript{7} Individually, furosemide has been demonstrated to accelerate left ventricular dysfunction and cardiac fibrosis\textsuperscript{8} in a porcine model. Meanwhile, thiazides are known to promote hyperglycaemia through worsening of insulin resistance, inhibition of glucose uptake, and decreased insulin release.\textsuperscript{9} These drawbacks may contribute to the link between diuretic use and negative outcomes. This is despite their noted benefits in terms of symptom control.\textsuperscript{3}

**PROGNOSIS OF DIURETIC THERAPY IN HF**

Several small studies have reported high dose loop diuretic therapy to be an independent predictors of increased all-cause mortality and hospitalisation for HF deterioration, with discharge prescriptions ≥40 mg being associated with these adverse clinical outcomes.\textsuperscript{10,11} This trend of worsening prognosis with higher doses of loop diuretics, appears to hold true for patients prescribed established GDMT (including angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), mineralocorticoid receptor blockers (MRA) and beta-blockers (BB)).\textsuperscript{3} However, this association could also reflect HF severity/progression. For example, diuretic dose can increase as cardiovascular disease progresses. This can be due to increased fluid retention, with subsequent reduced diuretic bioavailability, and/or the development of diuretic resistance.\textsuperscript{12,13} This combined with a progressive decline in cardiac function can lead to an increasing diuretic dosage.\textsuperscript{14} Therefore, this controversial association between higher diuretic dose and adverse outcomes, could reflect a selection bias for increased risk, rather than being a true independent risk. Nonetheless, the potential for diuresis and in particular excess diuresis to activate deleterious neurohumoral systems may also explain this association.\textsuperscript{12,13} Furthermore, it is important to emphasize that there may be differences between the loop diuretics in their effects on fibrosis, and perhaps other actions. For example, given its apparent superior anti-fibrotic, neurohormonal and pharmacological benefits compared to other loop diuretics, torsemide may not share these adverse clinical outcomes.\textsuperscript{15,16} The ongoing TRANSFORM-HF trial is currently evaluating this concept.
Given this possible link to an adverse prognosis, we should at every patient encounter assess whether a reduction in diuretic dose is feasible, without exposing the patient to the risk of rebound volume retention. While theoretical, this clinical goal should have been facilitated to date with the development of effective GDMT in HFrEF, through improved prognosis and cardiac function. However, it is possible that all of the beneficial effects of GDMT in HF are entirely distinct from salt and water retention or enhanced diuresis. Meanwhile, higher diuretic doses may simply represent disease severity, explaining the link to poor outcomes, as stated above.14-17

DIURETIC THERAPY IN PERSPECTIVE OF GDMT AND LITERATURE REVIEW

A few small trials, and the analysis of the European Society of Cardiology Heart Failure Long-Term registry, have demonstrated the feasibility of down-titration of diuretic therapy in certain patients on combination GDMT.6-8-10 Yet, there are few data detailing the impact of individual RAAS-modifying therapies or BB therapy on diuretic use. A summary of the available information and potential of the diuretic sparing effects of currently available and emerging therapies is outlined in Figure 1 and Table 1. For example, while ACEi demonstrate haemodynamic benefits, the report of their effect on diuretic therapy is largely limited to small studies, with variable results, particularly in the case of captopril.3,11-13 Similarly, in the case of MRAs, robust evidence of their effect on diuretic prescription in chronic HF is modest. This is somewhat surprising given its known diuretic effect on renal collection ducts, which is evident in patients with decompensated cirrhosis, in whom much higher doses of MRA are used in comparison to HF patients.27 The recent EPHESUS sub-study28 appears to be the only body of work to describe a significant loop diuretic dose reduction in patients taking eplerenone. These effects were noted at 90 days and beyond, resulting in a net reduction of loop diuretic dose of 2.2 mg/day. Further studies investigating the use of high dose MRAs in acute decompensated HF patients have demonstrated mixed results on

| Drug class         | Evidence of effect on diuretic dose | Potential effect on diuretic dose | Potential mechanism of action                                                                 |
|--------------------|-------------------------------------|----------------------------------|------------------------------------------------------------------------------------------------|
| ACEi               | ?                                   | ↑/↓                              | Beneficial neuroendocrine impact                                                                |
| ARNi              | Y                                   | ↓                                | Preservation of NP, in particular ANP                                                            |
| BB                 | ?                                   | ↑/↓                              | Initial negative inotropy may require increase, but long term benefit on ventricular function may cause a decline in diuretic need. |
| MRA                | Y                                   | ↓                                | Diuretic like effect and improved cardiac status                                                |
| SGLT2i             | ?                                   | -/↓                              | Blockade of Na+/glucose co-transporter and regulation of the renal Na+/H+ channel                |
| Guanylate cyclase modulators | ?                        | ?                                | Potentiate effects of natriuretic peptides and nitric oxide                                    |

Figure 1. Central illustration.
ACEi = ace inhibitor; ANP = atrial natriuretic peptide; ARNi = sacubitril/valsartan; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; NP = natriuretic peptide; SGLT2i = sodium glucose transport 2 inhibitor; Y = yes, ↑ = increase; ↓ = decrease; - = no change; ? = unclear.
### Table 1. Summary of available information of the diuretic sparing effects of currently available and emerging therapies

| Study | Author | Design | No. of patients | Active drug | Comparator | Follow-up | Diuretic effect |
|-------|--------|--------|-----------------|-------------|------------|-----------|----------------|
| ESC-EORP Heart Failure Long-Term Registry | Kapelios et al. | Prospective observational study | 8,130 | GDMT | - | 12 months | LD dose was increased in 16%, decreased in 8.3% and unchanged in 76% |
| - | Phariti et al. | Retrospective, single-centre review | 322 | Sacubitril/valsartan | - | 27 months | LD dose decrease was achieved in 37.2% of patients. Mean reduction of 10±38 mg furosemide equivalent across the entire population |
| ReBIC | Rohde et al. | Prospective, randomized and double-blind protocol | 188 | GDMT | Furosemide withdrawal | 90 days | 75.3% in the withdrawal group and 83.7% in the maintenance group were free of furosemide reuse during follow-up |
| NCT02288819 | Martens et al. | Prospective study, double blind | 50 | GDMT | Placebo | 180 days | Down-titration of LD was successful in 62% (n=37) Furosemide was increased in 2 patients on placebo and in 1 patient on enalapril |
| - | Webster et al. | RCT, double blind | 20 | Enalapril | Placebo | 12 weeks | Diuretic reduced in 33% of enalapril patients and increased in 5.6%. Placebo saw 39% of patients with diuretic increased |
| - | Franciosa et al. | RCT | 36 | Enalapril | Placebo | 3 months | 22% of captopril treated patients had reductions in diuretic dosage, as did 7% placebo-treated patients |
| - | Captopril Multicenter Research Group | RCT | 92 | Captopril | Placebo | 12 weeks | Captopril treatment led to a mean furosemide equivalent dose reduction of −2.2 mg/day (−2.9 to −1.6) throughout the follow-up |
| EPHESUS | Ferreira et al. | Post hoc analysis | 6,663 | Eplerenone | Placebo | 1.3 years | Eplerenone treatment led to a mean furosemide equivalent dose reduction of −2.2 mg/day (−2.9 to −1.6) throughout the follow-up |
| - | Ferreira et al. | Single blind trial | 100 | Spironolactone | Standard ADHF care | 3 days | Spironolactone led to earlier transition to oral LD (44% vs. 82%) |
| ATHENA-HF | Butler et al. | Post hoc analysis of RCT | 360 | Spironolactone | Standard ADHF care | 96 hours | No congestion or effect on diuretic dose observed |
| ATHENA-HF | Greene et al. | Post hoc analysis of RCT | 360 | Spironolactone | Standard ADHF care | 96 hours | No congestion or effect on diuretic dose observed |
| MADIT-CRT | Penn et al. | Post Hoc analysis of RCT | 1,610 | CRT-D | ICD | 1 year | 9.7% of patients had their diuretic stopped |
| - | Martens et al. | Retrospective | 648 | CRT | - | 6 months | 36% were able to tolerate down-titration of loop diuretics after CRT-implant |
| Paradigm | Vardeny et al. | Post hoc analysis | 8,399 | Sacubitril/valsartan | Enalapril | 24 months | Patients treated with sacubitril/valsartan were more likely to reduce diuretic dose and less likely to increase diuretic dose |
| - | Wachter et al. | Retrospective cohort study | 26,191 | Sacubitril/valsartan | - | 12 months | The mean daily LD dose decreased by 25% after initiation of sacubitril/valsartan |
| DAPA-HF | Jackson et al. | Post hoc analysis of RCT | 4,616 | Dapagliflozin | Placebo | 18 months | Diuretic dose did not change in most patients during follow-up, and mean diuretic dose did not differ between the dapagliflozin and placebo groups after randomization |
| RECEDE-HF | Mordi et al. | Post hoc analysis of RCT | 23 | Empagliflozin | Placebo | 6 weeks | 5 patients required a 41.7% reduction of their furosemide dose whilst on the active treatment arm of empagliflozin by day 3 |
| - | Shirakabe et al. | RCT | 60 | Empagliflozin | Placebo | 6 months | LD reduction in 54% of patients within 3 months |

ADHF = acute decompensated heart failure; CRT = cardiac resynchronization therapy; GDMT = guideline directed medical therapy; ICD = implantable cardiac defibrillator; LD = loop diuretic; RCT = randomised control trial.

These results suggest that the benefit of the MRA may be through improvement in cardiac function rather than a potent diuretic impact.**29**

BB use, through negative inotropy, may initially increase natriuretic peptides levels, as well as the need for diuretics.**32** Overtime, with improved cardiac function, diuretic need may decline.**33-37** Yet, neither the well-described initiation effects, nor the longer-term benefits of BB in HFrEF have been clearly associated with significant change in diuretic need.

However, some evidence for diuretic reduction with newer device-based intervention have been demonstrated in trials investigating cardiac resynchronization therapy (CRT). The retrospective MADIT-CRT sub-study**38** containing 507 subjects on baseline diuretic found...
that CRT implant led to diuretic cessation in 9.7% of patients. In a subsequent retrospective study of 352 subjects on baseline diuretics, 36% (126) of patients tolerated a down-titration of loop diuretic dose following CRT-implant. These effects appeared sustained and were associated with both an improved haemodynamic performance and decreased probability of HF or death.

In summary, despite the benefits of established GDMT and device-based therapies in HFrEF, the evidence of their impact on reducing diuretic requirement seems to be modest at best. The reason(s) for this observation are uncertain. One potential explanation is a possible underreporting of data on diuretic change, with little focus historically in clinical trials on the impact of a novel therapy on loop diuretic need. Another potential explanation could relate to the difficulty in clinically assessing volume status. This challenge could be undermining our confidence in altering, and especially reducing, diuretic dosage. Alternatively, it could be that the prognostic benefit of GDMT does not facilitate a reduction in diuretic dose, because of an interaction between the loop diuretic with the action of these agents. Supporting this is the observation that ACEi can antagonise the action of diuretics on the loop of Henle. Finally, it is possible, that if GDMT is not being optimally titrated, as outlined in the CHAMP-HF registry, that their effect on diuretic requirement is being blunted.

THE EMERGING RELATIONSHIP OF ANGIOTENSIN RECEPTOR ANTAGONISTS/NEPRILYSIN THERAPY WITH DIURETIC THERAPY

The recent approval of sacubitril/valsartan (angiotensin receptor-neprilysin inhibitor [ARNi]) in the management of HFrEF has provided a clear opportunity to reduce diuretic need in this phenotype of HF. Sacubitril/Valsartan, a first-in-class angiotensin type 1 receptor antagonist/neprilysin inhibitor, has already demonstrated a significant reduction in cardiovascular death, all-cause mortality, HF hospitalization, and improvement in quality of life. An additional important observation in this seminal trial involving over 8,000 patients was a reduction in diuretic therapy in approximately 20% of patients over the life-time of the study. Patients treated with this compound were also less likely to require diuretic increases.

In the post-licensing experience with this agent, similar observations have been made. Wachter et al. demonstrated a 25% mean reduction in diuretic dose during the first 6 months of treatment with an ARNi. Moreover, this diuretic effect occurred regardless of ARNi dose, but its magnitude was attenuated in those who had ARNi down-titrated. In our own experience of 322 patients switched from ACEi or ARB to ARNi, diuretic reduction was possible in 37.2%, with cessation of diuretic in 13.2% of patients. This translated to a mean reduction of 10mg of frusemide in the total population, which represented 17% of diuretic requirement. Of note, diuretic reduction was an independent predictor of achieving target dose of ARNi, shown in this population to be linked to improved clinical outcomes. This observation potentially facilitates a reduced incidence of hypovolaemia. This could subsequently lead to prevention of hypotension and worsening renal indices, known barriers to ARNi up-titrations.

Based on the background presented above and in particular the unremarkable impact of other pharmacological therapies on diuretic need, the data demonstrated with ARNIs raise the question of a specific impact of this compound on diuretic need. For example, through
nephrilysin inhibition, an ARNi increases circulating levels of natriuretic peptides,\(^6\)-\(^{48}\) in particular atrial natriuretic peptide (ANP).\(^{49}\) ANP increases the glomerular filtration rate,\(^{49}\)\(^{51}\) reduces sodium reabsorption in the inner medullary collecting duct,\(^52\) and can inhibit both the angiotensin II induced vasopressin release from the posterior pituitary, and the V2 receptor mediated action of vasopressin in the collecting ducts.\(^{53}\)-\(^{55}\) All the above could contribute to a significant diuresis, with a likely prompt early clinical affect. Indeed, this early “diuretic” impact may explain the impressive early reduction in HF rehospitalisation seen with ARNi.\(^{43}\) In addition, the documented improvement in ventricular function observed with ARNi over time may allow for a further delayed reduction in diuretic.\(^{56}\) Whatever the mechanism(s), the significant effect of ARNi on diuretic need in HFrEF patients is an important observation, and contrasts with the observations on other GDMT.

EMERGING HF THERAPIES AND THEIR POTENTIAL EFFECTS ON DIURETIC THERAPY

This reduction in loop diuretic need may not be confined to the ARNi compound. The emerging use of sodium glucose transport 2 inhibitors (SGLT2i) in HF may also provide an avenue for the reduction in diuretic need. Early clinical trials on SGLT2i demonstrated reduced incidence of new-onset HF among diabetic patients.\(^{57}\) The recent DAPA HF trial\(^{58}\) and EMPEROR-Reduced trials\(^{59}\) have demonstrated exciting new observations with this therapy (dapagliflozin and empagliflozin) in HFrEF, noting a reduction in cardiovascular mortality and ADHF admissions. Interestingly, this beneficial effect was observed in both diabetic and non-diabetic patients. Although the exact mechanism(s) driving these effects are unclear and possibly multifactorial. SGLT2i’s possess a well-described diuretic effect. By blocking the Na+/glucose co-transporter and regulating the renal Na+/H+ channel in the proximal tubule, a natriuresis occurs resulting in an osmotic diuresis.\(^{57}\) However, recent work has demonstrated that the SGLT2i’s diuresis is likely part of a homeostatic mechanism of body fluid volume maintenance. The net result of this diuresis is a minimal intravascular volume change, but a reduction in extracellular volume in patients with fluid retention.\(^{60\text{-}62}\) This may explain the recent post hoc analysis of the DAPA HF study demonstrating no significant change in loop diuretic dosage with SGLT2i use. However, a trend towards volume depletion was seen.\(^{63}\) This would suggest the benefit of SGLT2is are independent of diuretic therapy.\(^{64}\) In contrast, the much smaller RECEDE-CHF sub study\(^{65}\) demonstrated a 50% reduction in diuretic dose in 42% of patients taking empagliflozin, within 3 days. Another small prospective trial demonstrated a loop diuretic reduction in 54% of patients within 3 months.\(^{66}\) Future work is required to clarify the true magnitude of these observations and subsequent interactions with traditional diuretics. More recently, with the positive results of Vericiguat in reducing cardiovascular death or HF hospitalisation in the VICTORIA trial,\(^{67}\) it will be interesting to see what impact guanylate cyclase modulators could have on diuretic dosage. Nitric oxide and natriuretic peptides exert their biological effects by binding to membrane-associated guanylate cyclase receptors.\(^{35}\) Theoretically, a guanylate cyclase stimulator, such as Vericiguat, could potentiate the downstream effects of natriuretic peptides and nitric oxide.\(^{35\text{-}40}\) These effects could aid in enhancing diuresis and reducing diuretic need. In addition, the induced venodilation may facilitate the tolerance of increased congestion without a need for further diuretic dose increases.

The above holds promise for a reduction in the reliance on diuretics in HFrEF. Similar observations have not yet been made in the management of HF with Preserved Ejection Fraction (HFpEF). Diuretic therapy remains a cornerstone of therapy in this phenotype of HF,
and again is associated with the same negative effects observed in patients with HFrEF. The pathophysiology of HFpEF is different, and to date no effective disease modifying therapy has been discovered. There was some anticipation that the ARNi might be a breakthrough in this regard. While the PARAGON\textsuperscript{58} trial demonstrated a strong trend towards significance for its primary efficacy endpoint, there was a more encouraging signal with regards improvements in quality of life, symptoms and reduced hospitalisations for HFpEF patients. This benefit was particularly highlighted amongst female patients and patients with an ejection fraction of up to 57%. Moreover, Cunningham et al.\textsuperscript{69} in a sub-analysis, demonstrated a significant decrease in N-terminal fragment of proBNP in both men and women. This may possibly reflect decrease myocytes stretch, and thus, a decrease in intracardiac volume. Information on a reduction in diuretic need is not yet available. Similarly, we await the impact of SGLT2i on HFpEF and in particular, if there is any effect on diuretic need. Data from the CANVAS trial\textsuperscript{70} does indicate that SGLT2 inhibition may prevent the development of HFpEF. It is possible that the “diuretic impact” of these agents is an explanation for this observation. The ongoing DELIVER trial looking at dapagliflozin in HFpEF will be of interest in this regard. Finally, following the encouraging results from VICTORIA,\textsuperscript{67} further study of this agent in HFpEF will be directed at determining its impact on clinical or patient based outcomes. An effect on diuretic requirements would be a secondary and tangential outcome of future trials.

CONCLUSION

In conclusion, while diuretics remain the cornerstone of maintaining euvolemia in all HF phenotypes, their use is somewhat a “double-edged” sword. The impact of long-standing proven GDMT on diuretic need has been somewhat disappointing. In contrast the impressive impact of the recently licensed ARNi on diuretic reduction is encouraging. Further benefits in this regard may be observed with the emerging use of SGLT2 inhibition and guanylate cyclase modulators. These developments further highlight the clinical importance to continually assess each patient’s individual diuretic requirements through careful volume assessment. These skills are likely to become even more pertinent given the potential that exists for SGLT2i and indeed guanylate cyclase modulators to alter volume status. These agents could further impact diuretic therapy, bringing additional prognostic, symptomatic and quality of life benefit to this cohort.

REFERENCES

1. Kapelios CJ, Malliaras K, Kaldara E, Vakrou S, Nanas JN. Loop diuretics for chronic heart failure: a foe in disguise of a friend? Eur Heart J Cardiovasc Pharmacother 2018;4:54-63. PUBMED | CROSSREF
2. de Peuter OR, Lip GYH, Souverein PC, et al. Time-trends in treatment and cardiovascular events in patients with heart failure: a pharmacosurveillance study. Eur J Heart Fail 2011;13:489-95. PUBMED | CROSSREF
3. Huang X, Dorhout Mees E, Vos P, Hamza S, Braam B. Everything we always wanted to know about furosemide but were afraid to ask. Am J Physiol Renal Physiol 2016;310:F958-71. PUBMED | CROSSREF
4. Lachance P, Bagshaw SM. Loop and thiazide diuretics. In: Ronco C, Bellomo R, Kellum J, Ricci Z, editors. Critical Care Nephrology. 3rd ed. Philadelphia: Elsevier; 2017. p.358-64.
5. Ter Maaten JM, Martens P, Damman K, et al. Higher doses of loop diuretics limit uptitration of angiotensin-converting enzyme inhibitors in patients with heart failure and reduced ejection fraction. Clin Res Cardiol 2020;109:1048-59. PUBMED | CROSSREF
6. Kapelios CJ, Laroche C, Crespo-Leiro MG, et al. Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP Heart Failure Long-Term Registry. Eur J Heart Fail 2020;22:1424-37.

7. López B, Quequejeta R, González A, Sánchez E, Larman M, Diez I. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. J Am Coll Cardiol 2004;43:2028-35.

8. McCurley JM, Hanlon SU, Wei SK, Wedam EF, Michalski M, Haigney MC. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. J Am Coll Cardiol 2004;44:1301-7.

9. Rehman A, Setter SM, Vue MH. Drug-induced glucose alterations part 2: drug-induced hyperglycemia. Vol. 24. Diabetes Spectr 2011;24:234-8.

10. Martins J, Lourenço P, Araújo JP, et al. Prognostic implications of diuretic dose in chronic heart failure. J Cardiovasc Pharmacol Ther 2011;16:185-91.

11. 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.

12. Wilcox CS, Testani JM, Pitt B. Pathophysiology of diuretic resistance and its implications for the management of chronic heart failure. Hypertension 2020;76:1045-54.

13. Brater DC. Diuretic therapy. N Engl J Med 1998;339:387-95.

14. Mielniczuk LM, Tsang SW, Desai AS, et al. The association between high-dose diuretics and clinical stability in ambulatory chronic heart failure patients. J Card Fail 2008;14:388-93.

15. Abraham B, Megaly M, Sous M, et al. Meta-analysis comparing torsemide versus furosemide in patients with heart failure. Am J Cardiol 2020;125:92-9.

16. Greene SJ, Mentz RJ. Potential advantages of torsemide in patients with heart failure: more than just a ‘water pill’? Eur J Heart Fail 2018;20:471-3.

17. Kapelios CJ, Kaldara E, Ntalianis A, et al. Lowering furosemide dose in stable chronic heart failure patients with reduced ejection fraction is not accompanied by decompensation: a randomized study. Int J Cardiol 2014;177:690-2.

18. Phariri RB, Ferre-Vallverdu M, Maisel AS, et al. Sacubitril-valsartan in a routine community population: attention to volume status critical to achieving target dose. ESC Heart Fail 2020;7:158-66.

19. Rohde LE, Rover MM, Figueiredo Neto JA, et al. Short-term diuretic withdrawal in stable outpatients with mild heart failure and no fluid retention receiving optimal therapy: a double-blind, multicentre, randomized trial. Eur Heart J 2019;40:3605-12.

20. Martens P, Verbrugge FH, Boonen L, Nijst P, Dupont M, Mullens W. Value of routine investigations to predict loop diuretic down-titration success in stable heart failure. Int J Cardiol 2018;250:171-5.

21. Motwani JG, Verbrugge FH, Boonen L, Nijst P, Dupont M, Mullens W. Value of routine investigations to predict loop diuretic down-titration success in stable heart failure. Int J Cardiol 2018;250:171-5.

22. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983;2:755-63.

23. Webster MW, Fitzpatrick MA, Hamilton EJ, et al. Effects of enalapril on clinical status, biochemistry, exercise performance and haemodynamics in heart failure. Drugs 1985;30 Suppl 1:74-81.

24. Franciosa JA, Wilen MM, Jordan RA. Effects of enalapril, a new angiotensin-converting enzyme inhibitor, in a controlled trial in heart failure. J Am Coll Cardiol 1985;5:101-7.
25. Good JM, Brady AJ, Noormohamed FH, Oakley CM, Cleland JG. Effect of intense angiotensin II suppression on the diuretic response to furosemide during chronic ACE inhibition. Circulation 1994;90:220-4.

PUBMED | CROSSREF

26. Nieminen MS, Kupari M. The hemodynamics effects of ACE inhibitors in the treatment of congestive heart failure. J Cardiovasc Pharmacol 1990;15 Suppl 2:S36-40.

PUBMED | CROSSREF

27. Masoumi A, Ortiz F, Radhakrishnan J, Schrier RW, Colombo PC. Mineralocorticoid receptor antagonists as diuretics: can congestive heart failure learn from liver failure? Heart Fail Rev 2015;20:283-90.

PUBMED | CROSSREF

28. Ferreira JP, Eschalier R, Duarte K, et al. Reduced diuretic dose in patients treated with eplerenone: data from the EPHEUS trial. Circ Heart Fail 2020;13:e006597.

PUBMED | CROSSREF

29. Ferreira JP, Santos M, Almeida S, Marques I, Bettencourt P, Carvalho H. Mineralocorticoid receptor antagonism in acutely decompensated chronic heart failure. Eur J Intern Med 2014;25:67-72.

PUBMED | CROSSREF

30. Butler J, Anstrom KJ, Felker GM, et al. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. JAMA Cardiol 2017;2:950-8.

PUBMED | CROSSREF

31. Greene SJ, Felker GM, Giczewska A, et al. Spironolactone in acute heart failure patients with renal dysfunction and risk factors for diuretic resistance: from the ATHENA-HF trial. Can J Cardiol 2019;35:1097-105.

PUBMED | CROSSREF

32. Gheorghiade M, Eichhorn EJ. Practical aspects of using beta-adrenergic blockade in systolic heart failure. Am J Med 2001;110 Suppl 7A:68S-73S.

PUBMED | CROSSREF

33. Loncar G, von Haehling S, Tahirovic E, et al. Effect of beta blockade on natriuretic peptides and copeptin in elderly patients with heart failure and preserved or reduced ejection fraction: results from the CIBIS-ELD trial. Clin Biochem 2012;45:117-22.

PUBMED | CROSSREF

34. van den Meiracker AH, Lameris TW, van de Ven LL, Boomsma F. Increased plasma concentration of natriuretic peptides by selective β1-blocker bisoprolol. J Cardiovasc Pharmacol 2003;42:462-8.

PUBMED | CROSSREF

35. Nakaoka H, Kitahara Y, Amano M, et al. Effect of beta-adrenergic receptor blockade on atrial natriuretic peptide in essential hypertension. Hypertension 1987;10:221-5.

PUBMED | CROSSREF

36. Fung JWH, Yu CM, Yip G, et al. Effect of beta blockade (carvedilol or metoprolol) on activation of the renin-angiotensin-aldosterone system and natriuretic peptides in chronic heart failure. Am J Cardiol 2003;92:406-10.

PUBMED | CROSSREF

37. Frantz RP, Olson LJ, Grill D, et al. Carvedilol therapy is associated with a sustained decline in brain natriuretic peptide levels in patients with congestive heart failure. Am Heart J 2005;149:541-7.

PUBMED | CROSSREF

38. Penn J, Goldenberg I, McNitt S, et al. Changes in drug utilization and outcome with cardiac resynchronization therapy: a MADIT-CRT substudy. J Card Fail 2015;21:541-7.

PUBMED | CROSSREF

39. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. 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.

PUBMED | CROSSREF

40. BayliSS J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17-22.

PUBMED | CROSSREF

41. Francis GS, Siegel RM, Goldsmith SR, Oliviari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med 1985;103:1-6.

PUBMED | CROSSREF

42. Kapelios CJ, Kaldara E, Ntalianis A, et al. High furosemide dose has detrimental effects on survival of patients with stable heart failure. Hellenic J Cardiol 2015;56:154-9.

PUBMED
43. McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
PUBMED | CROSSREF

44. Vardeny O, Claggett B, Kachadourian J, et al. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. Eur J Heart Fail 2019;21:337-41.
PUBMED | CROSSREF

45. Wachter R, Fonseca AF, Balas B, et al. Real-world treatment patterns of sacubitril/valsartan: a longitudinal cohort study in Germany. Eur J Heart Fail 2019;21:588-97.
PUBMED | CROSSREF

46. Nougué H, Pezel T, Picard F, et al. Effects of sacubitril/valsartan on natriuretic targets and the metabolism of natriuretic peptides in chronic heart failure: a mechanistic clinical study. Eur J Heart Fail 2019;21:598-605.
PUBMED | CROSSREF

47. Gros C, Souque A, Schwartz JC, et al. Protection of atrial natriuretic factor against degradation: diuretic and natriuretic responses after in vivo inhibition of enkephalinase (EC 3.4.24.11) by acetorphan. Proc Natl Acad Sci U S A 1989;86:7580-4.
PUBMED | CROSSREF

48. Northridge DB, Newby DE, Rooney E, Norrie J, Dargie HJ. Comparison of the short-term effects of candoxatril, an orally active neutral endopeptidase inhibitor, and frusemide in the treatment of patients with chronic heart failure. Am Heart J 1999;138:1149-57.
PUBMED | CROSSREF

49. Ibrahim NE, McCarthy CP, Shrestha S, et al. Effect of neprilysin inhibition on various natriuretic peptide assays. J Am Coll Cardiol 2019;73:1273-84.
PUBMED | CROSSREF

50. Veldkamp PI, Carmines PK, Inasco EW, Navar LG. Direct evaluation of the microvascular actions of ANP in juxtamedullary nephrons. Am J Physiol 1988;254:F440-4.
PUBMED | CROSSREF

51. Ogawa T, de Bold AJ. The heart as an endocrine organ. Endocr Connect 2014;3:R31-44.
PUBMED | CROSSREF

52. Theilig F, Wu Q. ANP-induced signaling cascade and its implications in renal pathophysiology. Am J Physiol Renal Physiol 2015;308:F1047-55.
PUBMED | CROSSREF

53. Inoue T, Nonoguchi H, Tomita K. Physiological effects of vasopressin and atrial natriuretic peptide in the collecting duct. Cardiovasc Res 2001;51:470-80.
PUBMED | CROSSREF

54. Matsukawa T, Miyamoto T. Angiotensin II-stimulated secretion of arginine vasopressin is inhibited by atrial natriuretic peptide in humans. Am J Physiol Regul Integr Comp Physiol 2011;300:R624-9.
PUBMED | CROSSREF

55. Wong PCY, Guo J, Zhang A. The renal and cardiovascular effects of natriuretic peptides. Adv Physiol Educ 2017;41:179-85.
PUBMED | CROSSREF

56. Januzzi JL Jr, Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. J Am Coll Cardiol 2011;58:1881-9.
PUBMED | CROSSREF

57. Verma S, McMurray JJ. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 2018;61:2108-17.
PUBMED | CROSSREF

58. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.
PUBMED | CROSSREF

59. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-reduced trial. Circulation 2021;143:326-36.
PUBMED | CROSSREF

60. Ohara K, Masuda T, Morinari M, et al. The extracellular volume status predicts body fluid response to SGLT2 inhibitor dapagliflozin in diabetic kidney disease. Diabetol Metab Syndr 2020;12:37.
PUBMED | CROSSREF

61. Masuda T, Muto S, Fukuda K, et al. Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. Physiol Rep 2020;8:e14360.
PUBMED | CROSSREF
62. Nakagawa Y, Kuwahara K. Sodium-glucose cotransporter-2 inhibitors are potential therapeutic agents for treatment of non-diabetic heart failure patients. J Cardiol 2020;76:123-31.

63. Jackson AM, Dewan P, Anand JS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. Circulation 2020;142:1040-54.

64. Docherty KF, Jhund PS, Inzucchi SE, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. Eur Heart J 2020;41:2379-92.

65. Mordi NA, Mordi IR, Singh IS, Mcrimmon RJ, Struthers AD, Lang CC. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the RECEDE-CHF trial. Circulation 2020;142:1713-24.

66. Shirakabe A, Matsushita M, Kiuchi K, et al. Empagliflozin administration can decrease the dose of loop diuretics and prevent the exacerbation of renal tubular injury in patients with compensated heart failure complicated by diabetes. Circ Rep 2020;2:565-75.

67. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med 2020;382:1883-93.

68. Emdin M, Aimo A, Castiglione V, et al. Targeting cyclic guanosine monophosphate to treat heart failure: JACC review topic of the week. J Am Coll Cardiol 2020;76:1795-807.

69. Cunningham JW, Vaduganathan M, Claggett BL, et al. Effects of sacubitril/valsartan on N-terminal pro-B-type natriuretic peptide in heart failure with preserved ejection fraction. JACC Heart Fail 2020;8:372-81.

70. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.