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

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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 euvolemia. While effective in this regard,

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The authors have no financial conflicts of interest.

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their use has the potential to adversely affect long term outcomes.[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.[2] They also continue to be used in the vast majority of patients in the outpatient setting.[2] The use of diuretics in the acute setting results in improvement of symptoms and haemodynamic measures, through natriuresis and prostaglandin mediated systemic venodilation.[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.[4] 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).[5] However, Kapelios et al.[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.[7] Individually, furosemide has been demonstrated to accelerate left ventricular dysfunction and cardiac fibrosis[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.[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.[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.[1][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).[1] 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.[12][13] This combined with a progressive decline in cardiac function can lead to an increasing diuretic dosage.[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.[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.[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)18-20)] 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)21-26)] 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-study[28)] 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.

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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.[6]	Prospective observational study	8,130	GDMT	-	12 months	LD dose was increased in 16%, decreased in 8.3% and unchanged in 76%
-	Pharithi et al.[18]	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.[19]	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.[20]	Prospective	50	GDMT	-	180 days	Down-titration of LD was successful in 62% (n=31)
-	Webster et al.[23]	RCT, double blind	20	Enalapril	Placebo	12 weeks	Frusemide was increased in 2 patients on placebo and in 1 patient on enalapril
-	Franciosa et al.[24]	RCT	36	Enalapril	Placebo	3 months	Diuretic reduced in 33%of enalapril patients and increased in 5.6%. Placebo saw 39% of patients with diuretic increased
-	Captopril Multicenter Research Group[22]	RCT	92	Captopril	Placebo	12 weeks	22% of captopril treated patients had reductions in diuretic dosage, as did 7% placebo-treated patients
EPHESUS	Ferreira et al.[28]	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.[29]	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.[30]	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.[31]	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.[38]	Post Hoc analysis of RCT	1,610	CRT-D	ICD	1 year	9.7% of patients had their diuretic stopped
-	Martens et al.[39]	Retrospective	648	CRT	-	6 months	36% were able to tolerate down-titration of loop diuretics after CRT-implant
Paradigm	Vardeny et al.[44]	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.[45]	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.[63]	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.[65]	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.[66]	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.

diuretic requirements.[29-31] These results suggest that the benefit of the MRA maybe through improvement in cardiac function rather than a potent diuretic impact.[28]

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.[39] These effects appeared sustained and were associated with both an improved haemodynamic performance and decreased probability of HF or death.[38][39]

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.[40-42] 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.[4] 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.[43] 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.[44]

In the post-licensing experience with this agent, similar observations have been made. Wachter et al.[45] 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.[18] 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-titration.

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

neprilysin inhibition, an ARNi increases circulating levels of natriuretic peptides,[46-48] in particular atrial natriuretic peptide (ANP).[49] ANP increases the glomerular filtration rate,[50][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.[60-62] 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][68] 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[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.[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[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,[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.

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