Congestion and Use of Diuretics in Heart Failure and Cardiomyopathies: A Practical Guide

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Short title: Management of congestion in heart failure

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Abstract

Purpose of the review: Heart failure is a highly prevalent condition caused by many different aetiologies and characterised by cardiac dysfunction and congestion. Once developed, congestion leads to signs (peripheral oedema) and symptoms (breathlessness on exertion), adverse cardiac remodelling, and an increased risk of hospitalisation and premature death. This review summarises strategies that could enable early identification and a more objective management of congestion in patients with heart failure.

Recent findings: For patients with suspected or diagnosed heart failure, combining an echocardiogram with assessment of great veins, lungs and kidneys by ultrasound might facilitate recognition and quantification of congestion, the management of which is still difficult and highly subjective.

Summary: Congestion is a one of the key drivers of morbidity and mortality in patients with heart failure and is often under-recognised. Use of ultrasound allows for a timely, simultaneous identification of cardiac dysfunction and multi-organ congestion; ongoing and future studies will clarify how to tailor diuretic treatments in those with or at risk of heart failure.

Introduction

Heart failure can be defined as cardiac dysfunction associated with salt and water retention, also known as congestion[1,2]. In most patients with heart failure, congestion develops gradually[3]. A reduced cardiac output activates the renin-angiotensin-aldosterone system (RAAS) and increases the secretion of a hormone called arginine vasopressin (AVP). These compensatory mechanisms cause sodium and water retention (RAAS)[4] and stimulate thirst (AVP)[5] to maintain blood pressure and perfusion to vital organs[3]. However, an expansion of circulating blood volume will exacerbate symptoms and signs of heart failure, dilate the left ventricle further and worsen mitral regurgitation, predispose to atrial and ventricular arrhythmias, and eventually lead to pulmonary hypertension and right ventricular dysfunction. At this point, many patients are usually admitted to the hospital for aggressive anti-decongestive treatments to prevent further clinical deterioration[6,7]**.**

Prevalence and outcome of clinical congestion

Many patients hospitalised with heart failure have severe symptoms and signs of congestion[8]. Data from the national heart failure audit conducted in England and Wales in 2019 and 2020 reported moderate or severe peripheral oedema in 56% of patients with acute heart failure[9]. Increasing severity of congestion at admission is associated with a longer hospital stay[10,11], persistent congestion at discharge[6], and a high risk of early re-hospitalisation and one-year mortality[7].

In modern cohorts of ambulatory patients with heart failure, the prevalence of clinical signs of congestion is much lower if compared to those hospitalised: only 14.2%, 9.7%, 9.5% and 7.9% of patients with heart failure and reduced left ventricular ejection fraction (HFrEF) enrolled in the PARADIGM-HF trial had peripheral oedema, distended jugular vein, third heart sound and pulmonary rales, respectively[12]; most (70%) were free of signs of congestion. In the American cohort of patients with heart failure with preserved ejection fraction (HFpEF) enrolled in TOPCAT, the presence of peripheral oedema was common (71%), but other signs were infrequent[13]. For patients with heart failure followed-up in primary care, clinical features of congestion are not associated with the severity of left ventricular systolic dysfunction[14] but rather with the aetiology of heart failure. For example, patients with heart failure of ischaemic aetiology are more likely to report more severe symptoms than those whose heart failure is due to other causes[15]. More consistently, clinical signs of congestion are associated with older age, higher levels of natriuretic peptides, a greater use of loop diuretics, and poor outcomes[16,17].

How can we detect and monitor congestion?

Signs and symptoms of heart failure have traditionally been considered an essential component of its diagnosis but are usually identified late and only when congestion is severe. Notably, many other conditions can lead to breathlessness on exertion or peripheral oedema; therefore, their sensitivity and specificity for detecting congestion due to cardiac dysfunction are very low[17]. A chest radiograph is routinely requested in those attending hospital with dyspnoea, but it is more valuable in excluding other reasons for breathlessness instead of diagnosing heart failure[18]. Natriuretic peptides are hormones secreted by the heart in response to pressure or fluid overload, and guidelines recommend measuring their levels to

determine the need for specialist evaluation[19]. When low, they exclude severe cardiac dysfunction and congestion and provide reassurance, while high levels indicate a more dangerous situation. However, considerable expertise is required to interpret their levels, as they are influenced by age, atrial fibrillation, renal function, sex and body mass index[20–25]. A recent meta-analysis of 19 trials (>4500 patients) suggests that serial assessment of natriuretic peptides might guide therapy and reduce the risk of heart failure hospitalisation (by 20%) and death (by 13%) in those with heart failure[26]. Other biomarkers associated with tissue oedema (adrenomedullin)[27] and congestion due to right ventricular dysfunction, haemodynamic stress and inflammation (CA-125)[28] might improve risk stratification and help to tailor treatments in those with heart failure, but more evidence is required to support the use of these strategies in routine clinical practice.

Echocardiography is a fundamental diagnostic test to identify the underlying cause of congestion and formulate an initial management plan for those with suspected heart failure. Once heart failure is confirmed, guidelines do not recommend serial echocardiographic evaluation unless there is suspicion of substantial clinical deterioration. In recent years, ultrasound has been increasingly used to quantify congestion rapidly, safely, and with a high precision, in many organs. A dilated inferior vena cava (IVC) with a reduced inspiratory collapse is a sign of elevated right atrial pressure and intravascular congestion[29]. Assessment of IVC by ultrasound provides important clinical and prognostic information in patients with acute or chronic heart failure and its serial evaluation might be used to track response to diuretics[30–34]. The diameter of the internal jugular vein, and its changes with respiratory manoeuvres, can be measured with a linear ultrasound probe in any patient with heart failure, with good reproducibility[35]. In normal conditions, the resting diameter of the internal jugular vein increases more than four times during a Valsalva manoeuvre. A distended internal jugular vein diameter at rest with little or absent increase during a Valsalva correlates with more severe congestion and right ventricular dysfunction and identifies patients at greater risk of hospitalisation and death[36]. Sonographic assessment of the lung parenchyma helps to differentiate between cardiac and non-cardiac dyspnoea; thereby, it might facilitate a diagnosis of heart failure and pulmonary congestion[37]. With increasing interstitial fluids in the lungs, some vertical hyperechoic lines, called B-lines or comet-tail artefacts, can be visualised below the pleural line. Their increasing number is associated with a greater risk of hospitalisation or death in both in- and out-patients with heart failure[37,38]. Whether serial lung ultrasound can guide therapy and reduce congestion as well as the risk of future cardiovascular events is currently under evaluation; results are encouraging so far[39,40]. The assessment of renal venous flow can be added to this battery of ultrasonographic tests to improve identification of congestion and risk stratification[41].

Other non-invasive, low-cost technologies such as remote dielectric sensing (ReDS)[42], near-infrared spectroscopy (NIRS)[43], whole body bio-impedance and acoustic cardiography[44] can also quantify congestion in different organs and tissues. However, more data is required to understand their usefulness as diagnostic and monitoring tools in patients with heart failure.

For symptomatic patients with heart failure, invasive pulmonary artery pressure monitoring using implantable sensors might assist clinicians in managing congestion. In the recent GUIDE-HF trial, haemodynamic-guided management of congestion reduced heart failure hospitalisation but not mortality, and it remains unclear to whom this expensive technology should be offered[45,46].

Treatment options

In general, the management of congestion in patients with heart failure does not depend on aetiology or phenotype, and various therapies can be combined (Table 1, Figure 1).

1) Diuretics

Loop diuretics (furosemide, bumetanide, torasemide) are a cornerstone of treatment for congestion. They inhibit the sodium-potassium-chloride co-transporter in the thick ascending limb of the loop of Henle in the nephrons, causing increased sodium excretion, thereby enhancing diuresis. Loop diuretics can be administered either as repeated daily intravenous boluses or a continuous infusion[47] in those hospitalised with acute heart failure or, alternatively, as outpatient day case appointments[48]. The initial intravenous bolus is typically 40-50 mg of furosemide in those naïve to loop diuretics, whilst higher doses are frequently required in those already on oral formulations or with renal dysfunction. Early evaluation of urinary volume or sodium excretion might identify those in whom a dose intensification is warranted[47]. Novel furosemide formulations for subcutaneous administration are currently being developed and tested in clinical practice[49].

Loop diuretics have been used for many decades in ambulatory patients with heart failure; however, the level of evidence for their use is still based on expert opinion rather than on findings from randomised trials. Retrospective studies suggest a high risk of hospitalisation and death associated with their long-term use, particularly when higher doses are required to control refractory congestion[16]. Furosemide is the most used loop diuretic in clinical practice. TRANSFORM-HF, an open-label, pragmatic randomised trial that enrolled 2859 patients hospitalised with heart failure, did now show long term survival improvement with the use of torsemide vs furosemide (26.1% vs 26.2% respectively, p=0.77)[50].

Current guidelines recommend prescribing the lowest dose of loop diuretics that maintains euvolaemia[19]. A small, randomised trial (n=188 patients) conducted in Brazil suggested that many patients with HFrEF who were taking $\leq$80 mg furosemide/day and who had mild or no symptoms of congestion, were able to discontinue loop diuretics safely [51]. This is important in routine clinical practice, as tapering loop diuretic dosage or complete withdrawal might avoid exposure to unnecessary medications and potential side effects, while simultaneously allow the introduction and up-titration of other heart failure medications proven to improve clinical outcomes.

When loop diuretics are not sufficient to achieve adequate diuresis, the addition of another diuretic, e.g., a thiazide (or thiazide-like) diuretic, such as metolazone or bendroflumethiazide, could be effective[52]. However, this combination requires frequent renal function and electrolyte monitoring due to the increased risk of hypokalaemia, hyponatremia and a substantial drop in estimated glomerular filtration rate. A a recently reported single-centre, double-blind trial, that tested administration of hydrochlorothiazide 50 mg for three days in addition to loop diuretics in patients (n=51) admitted with acute heart failure, did not meet its primary endpoint of daily weight reduction[53]. Conversely, the larger multicentre, double-blind, placebo controlled CLOROTIC trial (230 patients) showed that addition of hydrochlorothiazide to loop diuretics might facilitate decongestion in patients admitted with an episode of heart failure, at the expense of a loss in renal function[54]. Amongst the other diuretics, acetazolamide has been receiving increasing attention in recent years due to its

capacity to block sodium reabsorption in the proximal convoluted tubule of the nephron. It has been hypothesised that its concomitant use with a loop diuretic might increase the efficacy of the latter[55]. Recently, Mullens and colleagues recruited 519 patients with acute heart failure in a double-blind, placebo-controlled trial that compared the addition of intravenous acetazolamide at a dose of 500 mg once daily, vs placebo, to loop diuretics. This trial showed that acetazolamide was safe and more effective than placebo in achieving successful decongestion (defined as the absence of signs of fluid overload within 3 days after randomisation)[56]; however, its use did not affect the secondary endpoint of mortality or rehospitalisation due to heart failure.

Mineralocorticoid receptor antagonists (MRAs – spironolactone and eplerenone) have a mild diuretic effect. More importantly, they reduce morbidity and mortality in patients with HFrEF[57,58] and perhaps even in those with higher left ventricular ejection fraction[59,60]. Unfortunately, their prescription is still sub-optimal[61,62]. Whether the mild diuresis associated with their use plays a significant role in reducing the risk of adverse cardiovascular outcomes is still unclear: MRAs might be cardioprotective via several other mechanisms, including, but not limited to, a favourable effect on cardiac preload and afterload, and collagen metabolism[63,64].

For patients with acute heart failure, the ATHENA-HF trial showed that adding high-dose spironolactone to the standard care for four days did not reduce N-terminal pro brain natriuretic peptide (NT-proBNP) levels, 30-day morbidity, or mortality when compared to the placebo[65]. Notably, no patients treated with high dose spironolactone developed hyperkalaemia ($K \geq 5.5$ mEq/L), which is thought to be a common side-effect associated with this treatment. Also, the proportion of patients receiving spironolactone who developed worsening kidney function (28%) was similar to those (32%) assigned to standard care ($p=0.42$). These findings may suggest that even higher doses might be required to unlock the potential diuretic effect of the MRAs.

There is some evidence that certain diuretics used as a treatment for hypertension might also prevent the development of overt clinical congestion and heart failure. In the ALLHAT trial, compared to amlodipine and lisinopril, chlortalidone decreased the risk of developing heart failure in those with hypertension and additional cardiovascular risk factors[66]. In the HYVET trial, which enrolled nearly 4,000 elderly individuals (mean age of 84 years, 60% female) who had a systolic blood pressure of 160 mmHg or higher, indapamide (with or without perindopril) led to a 64% reduction in the development of heart failure and reduced the risk of all-cause mortality by 21% after a follow-up period of 1.8 years[67]. In the HOMAGE trial, spironolactone at 50 mg/day decreased NT-proBNP and left atrial volume in patients with cardiovascular risk factors and pre-clinical congestion (raised NT-proBNP: 125-1000 ng/L) during nine months of treatment[68]. In FIGARO-DKD, the use of finerenone, a selective nonsteroidal MRA, decreased the risk of various heart failure outcomes in patients with type 2 diabetes mellitus complicated by chronic kidney disease and albuminuria (n=7352, 15% on loop diuretics), irrespective of baseline heart failure (7.8%) [69].

2) Sodium-Glucose Transport Protein 2 inhibitors (SGLT2i)

SGLT2i block the reabsorption of glucose from the proximal convoluted tubule of the nephron, thereby causing glycosuria, which in turn leads to osmotic diuresis[70], lower left ventricular filling pressures[71], and a decreased plasma volume[72]. The role of SGLT2i on sodium

handling is unclear at present in patients with heart failure, even though natriuresis has been proposed as one of the mechanisms by which SGLT2i might improve long-term outcomes in heart failure[73]. Using a placebo-controlled, crossover study design, Griffin and colleagues found that empagliflozin increased fractional excretion of sodium, and enhanced natriuresis when combined with an intravenous bolus of bumetanide in 20 patients with heart failure and type II diabetes[74]. In contrast, in RECEDE-CHF, empagliflozin increased 24-hour urinary volume within six weeks of treatment (the primary outcome) compared to placebo, but without a significant increase in 24-h urinary sodium excretion or fractional sodium excretion[75]. Lack of strict control on salt or fluid intake might explain these different results. More recently, in the small mechanistic, open-label DAPASALT study, 14 days of treatment with dapagliflozin in patients with type II diabetes and an estimated glomerular filtration rate between 91-130 mL/min/1.73m^2 on a controlled sodium diet (150mmol/day), significantly reduced systolic blood pressure without any effect on urinary sodium excretion[76]. In clinical practice, patients might require a lower dose of loop diuretics after initiating an SGLT2i, to avoid risks of volume depletion[77].

The benefits of SGLT2i for ambulatory patients with HFrEF are well established; increasing evidence suggests that SGLT2i might improve congestion in those with acute heart failure. Damman and colleagues performed a randomised, double-blind pilot trial where 80 patients with acute heart failure were randomised to empagliflozin 10mg/day or placebo within 24 hours of presentation to the hospital[78]. Compared to placebo, empagliflozin did not change the primary outcomes of visual analogue scale dyspnoea score or NT-proBNP levels. In a pre-defined post hoc analysis, empagliflozin increased urinary output and, expectedly, fractional glucose excretion, but did not increase fractional sodium or urine osmolality[79]. In the EMPULSE trial (n=530), in-hospital initiation of empagliflozin (vs placebo) in patients with acute heart failure led to greater clinical benefits at 90 days, including an effective and rapid decongestion, and a lower rate of death (4.2% vs 8.3%)[80]. The safety and efficacy of early initiation of SGLT2i in stabilised patients with heart failure before or soon after hospital discharge are supported further by findings from the prematurely stopped SOLOIST-WHF trial[81].

3) Angiotensin receptor neprilysin inhibitors (ARNI)

Angiotensin receptor neprilysin inhibitors (ARNI) block both angiotensin receptors (valsartan) and neprilysin (sacubitril), an enzyme that degrades brain natriuretic peptide (BNP). The resultant increase in BNP leads to enhanced natriuresis and vasodilation[82]. The use of an ARNI provides substantial clinical benefits to patients with HFrEF[83]. Importantly, it decreases the need for loop diuretics when compared to enalapril[84]. In the PIONEER-HF trial, initiation of an ARNI in patients with acutely decompensated heart failure after clinical stabilisation was safe and, compared to enalapril, led to a greater decrease in plasma NTproBNP concentrations, thereby suggesting a rapid diuretic effect (within a week)[85].

4) Vaptans

AVP is secreted in response to hyperosmolality and hypovolaemia. One of its major roles is to maintain organ perfusion. AVP increases water reabsorption from the filtrate in the renal tubule into the circulation and, at high concentrations, also causes vasoconstriction.

Tolvaptan is an oral vasopressin receptor antagonist that improves weight loss[86] in those with worsening heart failure and congestion and might increase serum sodium levels [87,88], but its use has not been associated with improved outcomes in this population. Current guidelines recommend considering Tolvaptan only in congested patients with HF and hyponatremia[19].

Other possible interventions

Observational studies suggest that a higher salt intake might increase the risk of developing cardiac events compared to salt restriction in patients with heart failure[89,90]. A recent open-label trial that enrolled nearly 21000 participants with elevated cardiovascular risk profiles showed that replacing regular salt with salt-substitute (75% sodium chloride and 25% potassium chloride by mass) might prevent stroke and death, including that due to heart failure [rate ratio 0.88 (0.55–1.43)][91]. However, in another open-label, multicentre trial that enrolled 806 ambulatory patients with heart failure, a low-sodium intake diet (i.e., <1500 mg/day) did not lead to a lower rate of clinical events compared to usual care during a period of 12 months[92]. A common issue, reported in more than 40% of patients with heart failure, is low compliance to prescribed treatments that might lead to rapid disease progression and an increased rate of hospitalisations[93,94]. Educating, empowering, and offering remote support to patients with heart failure might improve adherence to medications and quality of care, thus translating into better outcomes[95]. Device therapy might offer some clinical advantages for selected patients with severe congestion resistant to medications or those with structural heart disease (for example, severe mitral or tricuspid regurgitation)[96].

Conclusion

Congestion is one of the primary drivers of outcomes in patients with heart failure but is often under-recognised and treated subjectively. Use of ultrasound allows for identification of cardiac dysfunction and quantification of intravascular, renal or pulmonary congestion: future studies will clarify how to best tailor treatment of congestion in those with or at risk of developing heart failure.

Declarations

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Conflict of Interest

Pierpaolo Pellicori reports personal fees from Pharmacosmos, Vifor, and Caption Health, payment of honoraria from AstraZeneca, support from Pharmacosmos for attending meetings, outside the submitted work.

Fraser Graham reports receipt of sponsorship from Pharmacosmos to attend an international meeting.

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

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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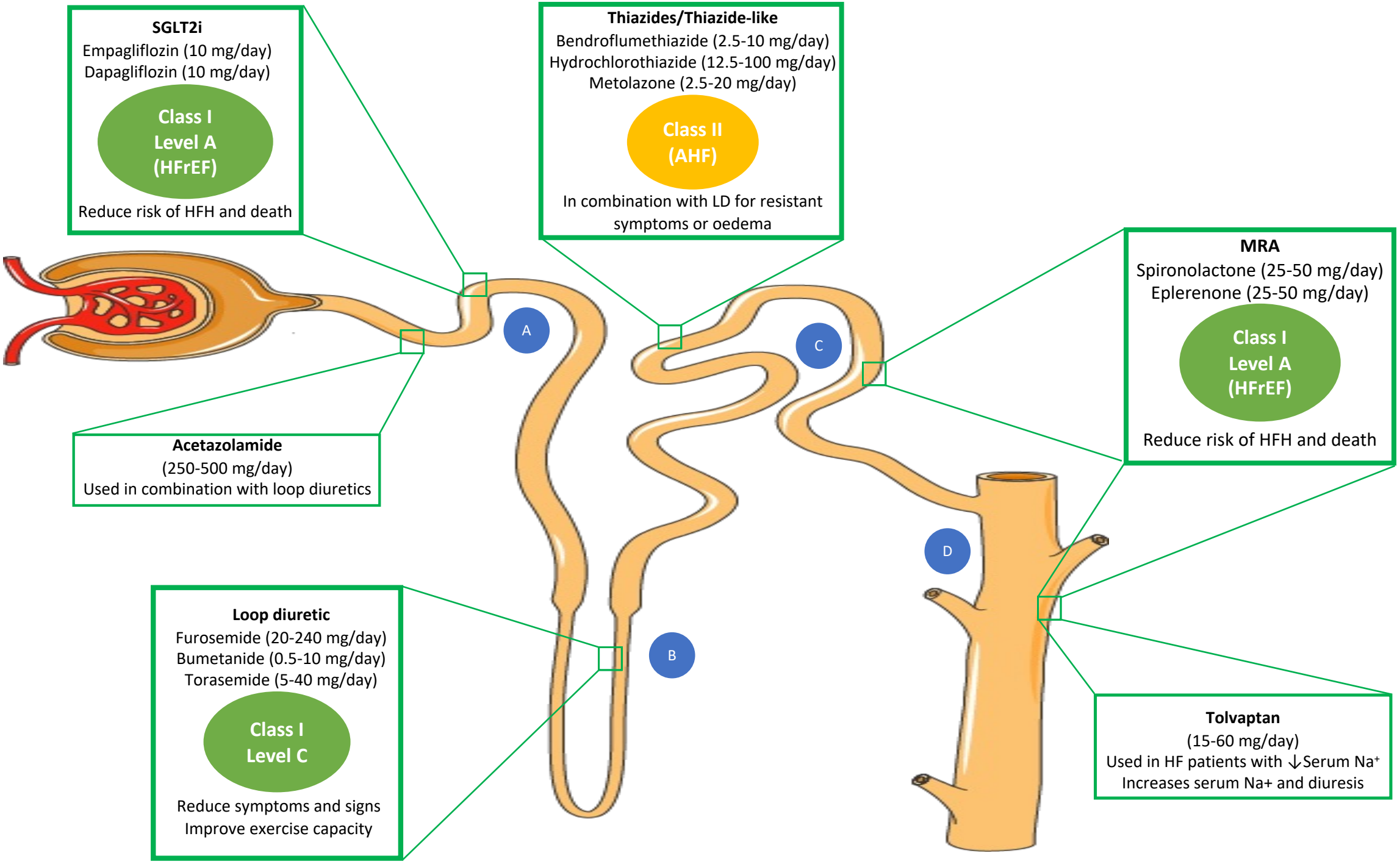
SGLT2i
Empagliflozin (10 mg/day)
Dapagliflozin (10 mg/day)
Class I
Level A
(HFrEF)
Reduce risk of HFH and death
Thiazides/Thiazide-like
Bendroflumethiazide (2.5-10 mg/day)
Hydrochlorothiazide (12.5-100 mg/day)
Metolazone (2.5-20 mg/day)
Class II
(AHF)
In combination with LD for resistant symptoms or oedema
MRA
Spironolactone (25-50 mg/day)
Eplerenone (25-50 mg/day)
Class I
Level A
(HFrEF)
Reduce risk of HFH and death
A
B
C
D
Acetazolamide
(250-500 mg/day)
Used in combination with loop diuretics
Loop diuretic
Furosemide (20-240 mg/day)
Bumetanide (0.5-10 mg/day)
Torasemide (5-40 mg/day)
Class I
Level C
Reduce symptoms and signs
Improve exercise capacity
Tolvaptan
(15-60 mg/day)
Used in HF patients with ↓Serum Na+
Increases serum Na+ and diuresis

Figure 1: Sites of action in a nephron, recommended doses, level of evidence and clinically observable effects of commonly used drugs for treatment of congestion in HF. *A*) *Proximal convoluted tubule* – SGLT2i bind to SGLT2 receptors and cause osmotic diuresis and natriuresis. Acetazolamide inhibits carbonic anhydrase and reduces reabsorption of bicarbonate from renal tubules and causes natriuresis and diuresis. *B) Thick ascending Loop of Henle* – Loop diuretics block the Na^+-K^+-$2Cl^-$ symporters and cause natriuresis, hypokalaemia and diuresis. *C) Distal convoluted tubule* – Thiazide/Thiazide-like diuretics block Na^+-Cl^- and cause diuresis and natriuresis. MRA block mineralocorticoid receptors and indirectly reduce Na^+ reabsorption and K^+ excretion, thus causing diuresis. *D) Collecting ducts:* - Tolvaptan blocks V2R and increase solute free water clearance, thus increasing serum Na^+. MRA block mineralocorticoid receptors.

Key: SGLT2i (Sodium-Glucose Transport Protein 2 inhibitors), HFrEF (heart failure with reduced ejection fraction), HFH (heart failure hospitalisation), AHF (acute heart failure), LD (loop diuretics), MRA (mineralocorticoid receptor antagonists), HF (heart failure), Na^+ (sodium), K^+ (potassium), Cl^- (chloride), V2R (vasopressin type 2 receptors)

Table 1: Drugs that might be used to treat congestion in patients with heart failure

Which?	When?	What is usual starting dose?	What is the usual maintenance dose?	What is the benefit?	What to look out for?	Level of evidence
Loop Diuretics (Furosemide, Bumetanide, Torasemide)	In patients with HF who have signs and symptoms of congestion	• In diuretic naïve patients: ▪ Furosemide: 20-40mg daily ▪ Bumetanide: 0.5-1mg daily ▪ Torasemide: 5-10mg daily • In patients already on a loop diuretic and hospitalised: at least IV equivalent of previous dose.	• Furosemide: 40-240mg daily • Bumetanide: 1-5mg daily • Torasemide: 10-20mg daily	Improvement in signs/symptoms Lifesaving in pulmonary oedema/AHF	Electrolyte disturbances (Hyponatraemia, hypokalaemia, hypomagnesaemia), dehydration, worsening renal function, hyperuricaemia/gout, postural hypotension	Class IC
Thiazide/Thiazide Like Diuretics (Metolazone, Bendroflumethiazide)*	In combination with LD for resistant symptoms or oedema	• Metolazone: 2.5mg alternate day • Bendroflumethiazide: 2.5mg daily	• Metolazone: up to 10mg daily • Bendroflumethiazide: up to 10mg 1-3 times/week	Improvement in signs/symptoms	Electrolyte disturbances (Hyponatraemia, hypokalaemia, metabolic alkalosis, hypercalcaemia), hyperglycaemia, hyperuricaemia, worsening renal function.	Class IIa (for AHF in combination with loop diuretics)
Mineralocorticoid Receptor Antagonists (Spironolactone, Eplerenone)	As soon as possible after diagnosis of HFrEF	25mg daily	25-50mg daily	Reduce CV morbidity and mortality in HFrEF, possibly beneficial also in higher LVEF.	Hyperkalaemia, worsening renal function, gynaecomastia and breast pain (Spironolactone), hypotension, decreased libido	Class IA (HFrEF)
SGLT2 inhibitors (Empagliflozin, Dapagliflozin)	As soon as possible after diagnosis of HFrEF	10mg daily	10mg daily	Reduce CV morbidity and mortality in HFrEF, reduce HFH in HFpEF	Euglycaemic ketoacidosis, urinary and genital infections Might reduce need of a loop diuretic Not approved for T1DM	Class IA (HFrEF)
Carbonic Anhydrase Inhibitor (Acetazolamide)*	In combination with LD for worsening symptoms or oedema	0.25g - 0.5g per day	0.25g - 0.5g per day	Improves congestion	Electrolyte disturbances, hypotension, paraesthesia, dysgeusia	
Vasopressin Receptor Antagonists (Tolvaptan)	Patients with HFrEF and hyponatremia (<135mmol/L)	15mg daily	Can be increased to up to 60mg daily.	It might improve diuresis, weight loss and serum sodium levels.	Blurred vision, increased thirst.	

Key: HF (heart failure), IV (intravenous), mg (milligram), AHF (acute heart failure), LD (loop diuretic), HFrEF (heart failure with reduced ejection fraction), CV (cardiovascular), LVEF (left ventricular ejection fraction), SGLT2 (Sodium-Glucose Transport Protein 2), HFH (heart failure hospitalisation), HFpEF (heart failure with preserved ejection fraction), T1DM (type 1 diabetes mellitus), g (gram), mmol (millimole)
*Evidence limited to small mechanistic trials.

Data extracted from [17,96,97].