Review

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# Congestion in Heart Failure: From the Secret of a Mummy to Today's Novel Diagnostic and Therapeutic Approaches. A Comprehensive Review

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*Review*

# Congestion in Heart Failure: From the Secret of a Mummy to Today's Novel Diagnostic and Therapeutic Approaches. A Comprehensive Review

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**Abstract:** This review paper presents a flashback on the evolution of the disease throughout the centuries, describes in summary pathophysiologic mechanisms, discusses briefly the mechanism of action of the diuretics, presents their role in decongesting heart failure patients and unfolds the data behind ultrafiltration in the management of acutely or chronically decompensated heart failure (ADHF), focusing on all the available data and advancements in this field. Acutely decompensated heart failure (ADHF) presents a critical clinical condition characterized by worsening symptoms and signs of heart failure, necessitating prompt intervention to alleviate congestion and improve cardiac function. Diuretics have traditionally been the mainstay for managing fluid overload in ADHF. Mounting evidence suggests that due to numerous causes, such as coexisting renal failure or chronic use of the loop diuretics, an increasing rate of diuretic resistance is noticed and needs to be addressed. There has been a series of trials that combined diuretics of different categories, without the expected results. Emerging evidence suggests that ultrafiltration may offer an alternative or adjunctive approach.

**Keywords:** Acute Decompensated Heart failure; fluid overload; loop diuretics; diuretic resistance; mineralocorticoid; SGLT2 inhibitors; ultrafiltration

## 1. Introduction and Background

Annual heart failure hospitalizations exceed 1 million in both the United States and Europe, and more than 90% are due to symptoms and signs of fluid overload. Additionally, up to 1 in 4 patients (24%) are readmitted within 30 days, and 1 in 2 patients (50%) are readmitted within 6 months [1]. Acute decompensated heart failure (ADHF) remains the leading cause of hospitalization in patients >65 years old and has the highest rate of 30-day rehospitalization among all medical conditions [2]. Recurrent fluid overload in heart failure has been associated with worse outcomes independently of age and renal function[3]. Deranged hemodynamics, neurohormonal activation, excessive tubular sodium reabsorption, inflammation, oxidative stress and nephrotoxic medications are important drivers of harmful cardiorenal interactions in patients with heart failure [4]. Central venous pressure elevation is rapidly transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure, which decreases net glomerular filtration [5]. Venous congestion itself can produce endothelial activation, up-regulation of inflammatory cytokines, hepatic dysfunction, and intestinal villi ischemia [6]. Thus, the foremost goal in managing acutely decompensated heart failure is to effectively resolve fluid overload[7].

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## 2. Heart Failure: Pathophysiology and Classification

Heart failure represents a clinical syndrome that consists mainly of symptoms like shortness of breath, orthopnea, ankle swelling and fatigue, that can be accompanied by signs of congestion like increased central venous pressure, pulmonary crackles or low limb edema[8]. It can be the result of either structural or functional abnormality leading to decreased cardiac output, increased intraventricular pressures and decreased tolerance to exercise. Coronary artery disease and diabetes mellitus have become the predominant predisposing factors for heart failure. Other structural causes of congestive heart failure (CHF) include hypertension, valvular heart disease, uncontrolled arrhythmia, myocarditis, and congenital heart disease. Finally, diastolic heart failure with impaired ventricular filling can also be caused by restrictive cardiomyopathy and constrictive pericarditis[9]. It has been shown that a major role in the decompensation of Heart failure is attributed to the inadequate drug treatment, failure to comply with the dietary sodium restriction, and decreased physical activity[10].

In the primary stages of congestive heart failure, heart muscle uses several compensatory mechanisms in order to maintain cardiac output in an attempt to keep up with the systemic demands. These mechanisms include changes in myocyte regeneration, myocardial hypertrophy and hypercontractility as well as the Frank-Starling mechanism increasing cardiac output. The increasing wall stress will force myocardium to compensate via eccentric remodeling leading to fibrosis and eventually affecting the loading conditions and wall stress[10].

The most commonly used heart failure classification is based on the left ventricle ejection function. The rationale behind this old classification is based on the fact that the treatment given has a bigger benefit to the lowest ejection fraction[11].

| **Heart Failure with reduced ejection fraction (HFrEF)** | **Symptoms +/- Signs** |
|---|---|
| | LVEF ≤ 40% |
| Heart Failure with mildly reduced ejection fraction (**HFmrEF**) | Symptoms +/- Signs |
| | LVEF 40 - 49% |
| Heart Failure with preserved ejection fraction (HFpEF) | Symptoms +/- Signs |
| | LVEF ≥ 50% |

Heart failure can present either as a chronically decompensated status (CHF), where the diagnosis is set and the symptoms build up throughout the years of the disease evolution or as an acute decompensation that could lead to a decrease in the cardiac output, either in a rapid or slow evolving pace. These two types necessitate the use of a decongesting treatment either in the conservative form with the use of diuretics either alone or with the aid of ultrafiltration.

Finally, NYHA classification categorizes heart failure patients according to their functional status starting from class I, where the patient is almost completely functional till class IV, where the patient has reached the last stage of the disease and unless transplanted or mechanically supported will have very poor prognosis.

| | |
|---|---|
| **Class I** | **No limitation of physical activity.Ordinary physical activity does not cause undue breathlessness,fatigue,or palpitations.** |
| Class II | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness,fatigue, or palpitations |
| Class II | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity results undue breathlessness,fatigue,or palpitations. |
| Class IV | Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken,discomfort is increased. |

### *2.1. Fluid Overload Significance*

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Fluid overload (FO) is a crucial and often central aspect of heart failure (HF) for several reasons. Understanding its importance in HF is fundamental to managing the condition effectively. Here are some key points highlighting its significance:

1. Symptom Severity: Fluid retention is a primary contributor to the hallmark symptoms of heart failure, such as dyspnea (shortness of breath), edema (swelling), and weight gain. As fluid accumulates in the lungs and peripheral tissues, the heart begins to fail followed by the kidneys.The kidneys respond by increasing the production of renin, leading to more aldosterone production, which is consequently followed by sodium and water retention[12] . In some patients, pulmonary congestion evolves rapidly because of a sudden increase in LV filling pressures. A precipitating factor is often recognised, like acute myocardial ischaemia, or uncontrolled hypertension. In this instance, the oedema is mainly present to the pulmonary airspaces (pulmonary oedema), while the total amount of fluid in the cardiovascular system remains unchanged[13].
2. Hemodynamic Disturbances: The accumulation of excess fluid in the body increases blood volume and venous pressure, resulting in intravascular and interstitial fluid volume expansion and redistribution. This, in turn, leads to elevated preload and afterload, negatively affecting cardiac function. Increased preload can worsen the workload of the heart muscle, further compromising its pumping efficiency. It has been described the concept of fluid redistribution which suggests that multiple factors like myocardial ischemia, episodes of high blood pressure, failure to comply with the pharmaceutical regimen, worsening renal function, and increased neurohormonal-sympathetic activation could increase venous tone and decrease venous capacitance, which in the setting of existing intravascular volume overload could only redistribute fluid from a peripheral venous reservoir like the splanchnic venous bed to the central cardiopulmonary circulation[14]. This results in the production of transudate fluid into the pulmonary alveolar space and the development of worsening dyspnea and symptomatic clinical congestion. This acute translocation of as much as 1 L of fluid, that will not alter the net body weight will cause pulmonary congestion and contribute to the overall discomfort experienced by HF patients.
3. Reduced Cardiac Output: Initially, compensatory mechanisms attempt to maintain cardiac output to meet systemic demands. These include myocardial hypertrophy, hypercontractility, apoptosis and regeneration of myocardial cells. The increased wall stress will lead to eccentric remodeling that further aggravates the loading conditions of the heart[15]. Due to decreased cardiac output the neuroendocrine system takes over releasing epinephrine, norepinephrine, endothelin - 1(ET-1) and vasopressin. The resulting vasoconstriction will lead to an increased afterload, which together with the increased levels of cyclic adenosine monophosphate (cAMP) and cytosolic calcium in myocytes, will further inhibit myocardial muscle from relaxing. The oxygen demand in the myocardium increases, necessitating further increase in cardiac output, leading to myocardial cell and apoptosis. The decreasing cardiac output will stimulate the renin-angiotensin-aldosterone system (RAAS), leading to increased salt and water retention, along with increased vasoconstriction. Moreover, RAAS releases Angiotensin II which is shown to increase myocardial cellular hypertrophy and interstitial fibrosis. This maladaptive function of angiotensin II increases myocardial remodeling[16]. This reduction in cardiac output can lead to inadequate oxygen delivery to the body's tissues, causing fatigue and exercise intolerance.
4. Kidney Function: Fluid retention can also impact kidney function. Inflammation and ischemia - reperfusion injury, will lead to endothelial injury and fluid overload, damaging the endothelial glycocalyx (EGL) and causing capillary leakage. This leakage will lead to interstitial edema and reduction in circulating intravascular volume, since volume to the interstitial compartment will be lost. This interstitial edema is the cause behind the acute kidney injury (AKI), as well as the progressive organ failure, due to the blockage of the lymphatic drainage and the poor interaction between cells[17] Finally, fluid overload causes atria distention and stretching of vessel walls, causing release of ANP and further damage to the EGL, aggravating the AKI[18] .This is a key contributor to the development of diuretic resistance, which is a

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common challenge in managing HF.Renal congestion increases renal tubular pressure, reducing glomerular filtration rate (GFR) and diuresis.

5. Electrolyte Imbalances: Fluid overload and diuretic therapy can lead to electrolyte imbalances, most commonly hyponatremia, hypokalemia, and hypomagnesemia[19]. The acid–base disturbances generally observed are metabolic alkalosis pure or combined with respiratory alkalosis[20]. Hyponatremia, which is the most common electrolyte abnormality observed in hospitalized subjects, is defined as a serum sodium concentration lower than 136 mmol/L[21]. Mild-to-moderate hyponatremia is generally present in 10 % of HF patients[22]. In OPTIME-CHF trial, 27 % of patients had serum sodium concentrations between 132 and 135 mEq/L[23], while in the ESCAPE trial, persistent hyponatremia, defined as serum sodium below 134 mEq/L, was present in 18% of the hospitalized patients. Hypokalemia is commonly observed in CHF patients, and it is a strong independent predictor of mortality[24] .Hypokalemia has not been well defined in HF, and even in the literature, its range varies from 3.5 to 4.0 mEq/L (mmol/L)[25] . Hypokalemia is generally more evident in patients with advanced CHF receiving intensive diuretic therapy and those whose renin–angiotensin system is highly activated[26]. Low levels of serum K+ may be a marker of increased neurohormonal activity and disease progression[27]. Diuretics and adrenergic stimulation may cause hypokalemia, while neurohormonal blockade using ACE inhibitors, angiotensin receptor blockers, beta-blockers, and aldosterone antagonists may cause hyperkalemia. This drug effects require frequent control of K+ in these patients[28]. The prevalence of hypomagnesemia in CHF subjects ranges from 7 % of well-compensated ambulatory patients to 52 % in more advanced CHF patients who are under aggressive diuretic treatment[29]. Magnesium deficiency, in animal models, alters mitochondrial structure with calcium accumulation, cell death, and multifocal myocardial necrosis[30]. There is confirmation that the effective correction of magnesium disturbances is favorable in CHF patients[31], mostly due to the reduction of potentially lethal arrhythmias. Diuretics (loop-acting diuretics in particular) produce most of the renal magnesium loss, especially in the volume-expanded setting of CHF[32].

Few cases of hypocalcemia (total serum calcium concentration <8.6 mg/dL or ionized calcium concentration <1.1 mmol/L) in CHF have been reported, often associated with hypomagnesemia[20]. Loop diuretics block the reabsorption of calcium in the loop of Henle and may play a role in the pathogenesis of hypocalcemia[33]. Correction of calcium disorder could improve CHF[34]. These imbalances can cause cardiac arrhythmias and muscle weakness, complicating the clinical picture in HF.

6. Mortality Risk: The severity of fluid retention is often linked to the prognosis of HF. Patients with more significant fluid overload tend to have a higher risk of mortality. Addressing fluid retention is, therefore, essential for improving patient outcomes.
7. Hospitalizations, readmissions and Quality of Life (QoL): Effective management of fluid overload can significantly enhance a patient's quality of life. Rehospitalization rate is a comprehensive measure of disease burden and progression. While the length of hospital stays has decreased over time in heart failure patients, readmission rates have essentially remained unchanged[. 35]. Congestion is the most frequent cause of readmission. Other factors associated with increased risk of readmission include higher age, comorbidities, premature discharge and noncompliance. Hospitalization is easy to identify and easy to quantify. Early readmission is associated with worse long-term outcomes and significant increases in heart-failure-related health costs. With each readmission, QoL declines [36].

In summary, fluid overload is central to the pathophysiology and clinical presentation of heart failure. It impacts symptoms, cardiac function, kidney function, and overall prognosis. Therefore, effective management of fluid is a cornerstone of heart failure treatment, emphasizing the need for an integrated approach that includes diuretics and other therapeutic interventions to address this critical aspect of the condition.

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*2.2. Congestion and Extracellular Fluid Overload (FO) Assessment*

It is of paramount importance to recognize and treat fluid overload (FO) since early treatment can prevent or ameliorate the adverse events caused by the extra volume build up. There are markers to be monitored in order to reveal and quantify the extra volume overload. Inflammatory markers (C-reactive protein, myeloperoxidase), markers suggestive of fibrosis and extracellular remodeling (procollagen, ST2, galectin-3), markers for mechanical strain/stretch (natriuretic peptides, CD146, carbohydrate antigen 125 [CA125]), markers of hemodynamic homeostasis (copeptin, adrenomedullin), tissue perfusion (lactate), and heart muscle injury (troponins)[37].

There is a clear association between the decrease of red blood cells concentration and plasma volume expansion. Increasing values of hematocrit has been suggested as a surrogate for plasma refill rate and decongestion rate[38]. Fujita et al. found that hemodilution during the first 3 days of hospitalization in patients with acute heart failure was associated with both increasing rates of pulmonary edema in comparison to those with hemoconcentration (85 vs. 63%, $p < 0.01$) and HF-related readmission rate (34 vs. 9%, $p < 0.01$)[39]. In PROTECT (Placebo-Controlled Randomized Study of the Selective Adenosine A1 Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study the rapid increase in hemoglobin concentration during the first 7 days of the hospitalization in patients presenting with acute decompensated heart failure was associated with a favorable outcome, despite the incidences of acute kidney injury(AKI) that were observed[40]. Low hemoglobin levels, however, should be interpreted with caution in order not to mistake dilution-related pseudo-anemia for true anemia, especially if under erythropoietin treatment[41].

Moreover, echocardiography is a useful tool in assessing the overall function of the heart. In the case of chronically decompensated heart failure, FO leads to pressure overload, which flattens the interventricular septum both in diastole and systole[42]. If the pressure overload occurs acutely, the septum is pushed during diastole causing the characteristic D - shaped left ventricle. The tricuspid regurgitation caused by the right ventricular enlargement will increase both the right atrial pressure and the central venous pressure (CVP)[43]. Inferior vena cava (IVC) ultrasound will reveal the diameter of the vessel and whether there is an IVC collapse during respiration. Volume depletion is considered with an IVC diameter <1.5 cm while an IVC diameter >2.5 cm suggests volume overload. An IVC diameter of ≤2.1 cm and collapsibility of >50% with a sniff indicates normal RAP of 3 mm Hg (0–5 mm Hg), an IVC diameter of >2.1 cm with <50% inspiratory collapse indicates high RAP of 15 mm Hg (10–20 mm Hg), and scenarios in between correspond to an intermediate value of 8 mm Hg (5–10 mm Hg)[44].

The increase in the right atrial pressure is also transmitted, through liver sinusoids, into the portal vein. While normal portal flow is continuous or only mildly pulsatile, in case of increased atrial pressure there is an increased pulsatility in portal venous flow[45]. This increase can be found in patients with increased systolic pulmonary pressure[46], right ventricular dysfunction[47] and increased intravascular volume[48]. Finally, a rise in NT-proBNP seems to be correlated with a rise in the portal vein pulsatility.

While chest X-ray, historically the first diagnostic tool in doctors' diagnostic algorithm, can show signs of lung congestion and pleural fluid, 20% of patients with congestion exhibit a normal chest X-ray[49]. Lung ultrasound has evolved over the last years as a trustworthy tool for ruling out interstitial oedema and pleural effusions. It detects B-lines originating from extravasated fluid into the interstitium and alveoli. The presence of more than three B-lines in more than two intercostal spaces bilaterally are thought to be sufficient in order to detect interstitial and alveolar oedema in acute heart failure. The sensitivity reaches almost 90%, but it lacks specificity since the described interstitial edema can have a non-cardiac origin. Equally sensitive but less specific is the mitral inflow E-wave velocity, with a value of >50 (cm/s) suggestive of pulmonary capillary wedge pressure (PCWP) > 18mmHg. The deceleration time of the mitral valve has high both the specificity and sensitivity reaching 80% but is affected by the same weakness with the mitral inflow E-wave velocity which is the more difficult diagnosis when there is fusion of the E and A wave[50].

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*2.3. Diuretic Agents*

Diuretics are medications that promote diuresis, commonly used to treat conditions such as hypertension, heart failure, and edema (fluid retention). There are several classes of diuretics, each with its mechanism of action and specific indications. Here's an overview of the main classes: loop diuretics, thiazide diuretics, potassium-sparing diuretics and carbonic anhydrase inhibitors:

Loop Diuretics (LD):

- Mechanism of Action: Loop diuretics act on the thick ascending limb of the loop of Henle in the nephron of the kidney. They inhibit the reabsorption of sodium and chloride ions, leading to increased diuresis.
- Indications: Loop diuretics are potent and are often used in the treatment of acute and severe conditions of fluid overload, such as acute heart failure, pulmonary edema, and edema associated with renal dysfunction.
- Common Medications: Examples of loop diuretics include furosemide, torsemide, and bumetanide.

Thiazide Diuretics (THZ):

- Mechanism of Action: Thiazide diuretics act on the distal convoluted tubules of the nephron. They inhibit sodium and chloride reabsorption, leading to increased urine production.
- Indications: Thiazide diuretics are typically used in the management of hypertension and mild to moderate edema. They are also sometimes used in the treatment of certain kidney stone conditions, such as calcium oxalate stones.
- Common Medications: Examples of thiazide diuretics include hydrochlorothiazide, chlorthalidone, and indapamide.

Potassium-Sparing Diuretics (MRA):

- Mechanism of Action: Potassium-sparing diuretics act on the distal tubules and collect ducts of the nephron. They promote diuresis while minimizing potassium excretion. Some potassium-sparing diuretics work by blocking the action of aldosterone, a hormone that typically promotes sodium and water retention while increasing potassium excretion.
- Indications: Potassium-sparing diuretics are often used in combination with other diuretics to help counteract the potassium loss associated with loop and thiazide diuretics. They are also used in conditions where retaining potassium is important, such as hypokalemia.
- Common Medications: Examples of potassium-sparing diuretics include spironolactone, eplerenone, and amiloride.

Carbonic anhydrase inhibitors (CAIs):

- Mechanisms of Action: Carbonic anhydrase inhibitors primarily target carbonic anhydrase isoenzyme II, which is found in the kidneys, eyes, and other tissues. The inhibition of carbonic anhydrase leads to several physiological effects:
  - Diuresis: In the kidneys, carbonic anhydrase inhibitors reduce bicarbonate reabsorption, leading to increased bicarbonate and water excretion, making them useful in conditions like edema and metabolic alkalosis.
  - Reduction of Intraocular Pressure: In the eyes, CAIs decrease the production of aqueous humor, making them a cornerstone in the treatment of glaucoma.

Therapeutic Applications:

- Edema: Systemic CAIs, like acetazolamide and methazolamide, are employed to manage edema in congestive heart failure, nephrotic syndrome, and high-altitude sickness.
- Metabolic Alkalosis: CAIs can be used to correct metabolic alkalosis by increasing renal bicarbonate excretion.

Side Effects and Considerations:

- Electrolyte Imbalances: CAIs can lead to hypokalemia and metabolic acidosis due to excessive bicarbonate excretion.

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- Renal Stones: Prolonged use of CAIs may increase the risk of developing kidney stones, particularly in patients prone to stone formation.
- Sulfonamide Allergies: Some CAIs, such as acetazolamide, contain a sulfonamide moiety, which can lead to allergic reactions in individuals with sulfonamide allergies.

*2.4. Anatomy of the Nephron and the Loop of Henle*

To comprehend how loop diuretics work, it's essential to have a basic understanding of the anatomy of the nephron, the functional unit of the kidneys. The nephron consists of various segments, and one of the key segments is the loop of Henle. This U-shaped tubule is divided into two limbs: the descending limb and the ascending limb.

The ascending limb further differentiates into the thin and thick ascending limbs. The thick ascending limb is the primary site of action for loop diuretics.

*2.5. Sodium-Potassium-Chloride Cotransporter (NKCC2)*

The thick ascending limb is lined with specialized cells that express a key transporter known as the Sodium-Potassium-Chloride Cotransporter 2 (NKCC2). This cotransporter actively reabsorbs sodium, potassium, and chloride ions from the tubular fluid into the kidney cells. The movement of these ions across the cell membrane is essential for maintaining electrolyte balance in the body.

*2.6. Mechanism of Loop Diuretics*

Loop diuretics, including drugs like furosemide, bumetanide, and torsemide, exert their effects by specifically inhibiting the NKCC2 transporter in the thick ascending limb of the loop of Henle.

8. Inhibition of NKCC2: Loop diuretics competitively inhibit the NKCC2 transporter. They do this by binding to the chloride-binding site of the cotransporter. As a result, the transporter's ability to reabsorb sodium, potassium, and chloride ions is significantly impaired.
9. Reduced Sodium Reabsorption: By inhibiting NKCC2, loop diuretics disrupt the normal process of sodium, potassium, and chloride reabsorption. This reduction in sodium reabsorption leads to a decrease in the osmotic gradient within the nephron, thus preventing the passive reabsorption of water that normally follows sodium reabsorption.
10. Increased Urine Output: The disrupted reabsorption of sodium and other ions results in a higher concentration of these ions in the tubular fluid. This increased osmotic load in the nephron prevents the reabsorption of water, promoting diuresis.

*2.7. Pharmacokinetics and Dose-Response:*

Bioavailability:

- Furosemide when administered orally exhibits limited and highly variable bioavailability[51]. When the kidney function is preserved, intravenous furosemide doses are almost twice as potent on a per milligram basis as oral doses. In acute decompensated heart failure, a higher peak level may be required, and an intravenous dose may be more effective.
- Torsemide's bioavailability can reach or exceed >90% in patients with renal insufficiency, liver cirrhosis, and heart failure[52]. Torsemide's bioavailability remains unchanged with food intake compared to the other two loop diuretics[53]. Torsemide's peak serum concentration is similar with the other two substances but has the longest half-life of about 3.5 hours versus 1 hour for furosemide and 2 hours for bumetanide[54]. Passive venous congestion in HF patients can lead to gut edema, which can cause a great variability in the diuretic effect mainly of furosemide[55] due to malabsorption.

Onset and Duration of Action:

- The onset of action is rapid, typically within 30 minutes of administration.
- The duration of action is relatively short, usually around 4 to 6 hours, necessitating multiple daily dosing.

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Dose-Response Curve:

- Loop diuretics exhibit a steep dose-response curve, especially at lower doses.
- Lower doses of loop diuretics can cause a significant increase in diuresis, leading to pronounced sodium and water excretion.
- As the dose increases, the diuretic effect reaches a plateau, and further increases in dose may not significantly enhance diuresis but may increase the risk of adverse effects.

## 3. Diuretics in Heart Failure: Historical Perspective

The first ever case of decompensated heart failure ever described belonged to 3,500-year-old mummified remains found in the Valley of the Queens by the Italian Egyptologist Ernesto Schiaparelli[56]. Andreas Nerlich, a pathologist from Germany, who performed the histologic examinations of the lungs concluded that the leading cause of death was pulmonary edema probably due to heart failure, after having excluded other causes of 'fluid in the air spaces of the lung like microbial respiratory infections or granulomas[57].

Over the centuries many civilizations managed to describe the presence of fluid accumulation, but without any understanding of the cause behind it[58], failing to make a connection between the symptom and the heart. The breakthrough occurred in 1918 when E.H. Starling[59] published his 'Law of the Heart'. The demonstration that increasing end-diastolic volume enhances cardiac performance contradicted the 19th century view that dilatation weakened the heart. Until the 1980s the treatment was based on fluid restriction, rest and use of digitalis and diuretics, underlying the clear orientation of the scientific community towards the kidney function rather than the one of the hearts. Heart failure will finally be recognised as a neuroendocrine disease in the 1980s and the treatment with diuretics, vasodilators and inotropes will be put under discussion as it would keep the patient hostage in the vicious circle of the endocrine response present in heart failure[60].

Years passed and many drug categories were added to the treatment of heart failure tackling all the aspects of the pathophysiology cataract of the disease like ACE inhibitors, ARNIs, b - blockers, MRAs and SGLT 2 inhibitors. The goal,however, of keeping the patient in a euvolemic status remains and this is exactly the treatment given when the patient decompensates besides the optimal medical treatment. Although routine diuretic treatment of heart failure may appear uncomplicated, questions about the optimal use of diuretics, particularly in settings of acute decompensated heart failure (ADHF) and diuretic resistance.

### *3.1. Challenges in Diuretic Therapy*

Heart-kidney disorders caused by variable etiologies and precipitated by factors such as hemodynamic, neurohormonal, and inflammatory disorders can lead to cardiorenal syndrome (CRS)[61]. The clinical profile is characterized by decreased glomerular filtration, sodium avidity, and diuretic resistance (DR)[62].

### *3.2. Diuretic Resistance (DR)*

Mortality, pump failure death and sudden death present independent association with diuretic resistance (DR). It may be defined as a non-satisfactory rate of diuresis/natriuresis despite adequate diuretic regimen[63]. Diuretic resistance definition includes persistent congestion, despite adequate and escalating doses of diuretic agents equivalent to ≥80 mg/day furosemide; the amount of sodium excretion as a percentage of filtered load below 0.2% and failure to excrete at least 90 mmol of sodium within 72 h of a 160-mg twice-daily dose of furosemide. Other proposed parameters include weight loss achieved per 40 mg of furosemide or equivalent; net fluid loss per milligram of loop diuretic agent; and natriuretic response to furosemide as urinary sodium-to-urinary furosemide ratio[64]. In HF patients, the prevalence of diuretic resistance (DR) is estimated as 20%-30%[65]. It is vital to differentiate the homeostatic mechanism of the kidneys to protect themselves from a hypovolemic status and present poor response to diuretics even in the naive to diuretics patients[66]. Diuretic efficiency integrates the diuretic response in context of the loop diuretic dose, dividing fluid output, weight

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change, or sodium output by the loop diuretic dose administered[67]. Diuretic efficiency is underscored in clinical practice since a modest response to a low-dose diuretic can result in good diuretic efficiency that is clinically unimportant if inadequate to bring the patient into euvolemic status. It was proposed to be a mechanism of resistance according to anatomic location and significance[68]. When extra tubular, the mechanism can be venous congestion, increased intra-abdominal pressure or kidney vasoconstriction and hypoperfusion, decreased cardiac output, hypoalbuminemia and high sodium intake. Even though gut edema and low duodenal blood flow do not typically affect furosemides oral bioavailability, they slow absorption, leading to reduced peak plasma levels, and therefore contribute to diuretic resistance. When tubular, it can be divided into the loop of Henle or post - loop of Henle. In the former, inadequate loop diuretic dose or rightward shift in loop diuretic dose response curve should be checked, while when the latter compensatory distal tubular sodium reabsorption, hypochloremic alkalosis or specific transporters should be controlled[69]. Finally, the extent of natriuresis following a defined dose of diuretics decreases over time, even in normal subjects. This is called the 'braking phenomenon' and it is the result of both haemodynamic changes at the glomerulus and adaptive changes in the distal nephron. Loop diuretics are 'threshold drugs. The dose-response curve is shifted downwards and right wise due to heart failure. In other words, a higher dose of loop diuretics is needed in order to achieve the same level of sodium excretion.

The clinical presentation of diuretic resistance consists in insignificant relief of symptoms, further decompensation of heart failure besides the in-hospital treatment, increased mortality post discharge and up to three times higher rate of rehospitalization[64]. In the Acute Decompensated Heart Failure National Registry (ADHERE) 33% of the 50000 patients enrolled that were treated with conventional diuretics lost around 2.3kgr, 16% gained weight while in hospital and half of them were discharged with persistent congestion[70]. Moreover, in the Diuretic Optimization Strategies Evolution (DOSE) trial 42% of participants with acute heart failure reached the end point of death or unprogrammed visit to the hospital at 60 days irrespective of the treatment followed[71].

### *3.3. Treatment Strategies to Tackle DR*

Once initiated, the effect of the diuretic treatment needs to be monitored. For this purpose, an indicator needs to be used easily in daily clinical practice. There are two indicators that are used currently, the net fluid output and body weight changes. Weight assessment is technically challenging, and fluctuations seen in weight during hospitalization might not represent changes in volume redistribution. To add to that, there is no clear correlation between fluid output and weight loss[72].

#### Loop Diuretics

Intravenous loop diuretics exert their effect within the first couple of hours and a return to baseline sodium excretion is noticed by 6–8 h. In this timeframe, early evaluation of the diuretic response can take place and will identify patients with a poor diuretic response[73,74]. It is known that thiazide and thiazide-like diuretics may partially overcome distal increased sodium avidity accompanied with chronic loop diuretic use[75]. In contrast to conventional knowledge, more recent evidence does support the effectiveness of thiazides in patients with a reduced glomerular filtration rate (< 30 mL/min)[76].

In the DOSE - AHF trial high loop diuretic dose, defined as 2.5 times the home dose and not less than 80 mg of furosemide per day, had a more favorable effect than the equal to home dose and this led to clinical improvement with dyspnea relief and decrease in body weight and extravascular volume[71]. Renal dysfunction, defined as an increase in creatinine by more than 0.3 mg/dL, occurred more in the high-dose group. However, this increase did not affect the outcome as it was shown by a post-hoc analysis of the DOSE-AHF trial[77]. Furthermore, a better outcome was seen in the high - dose group when adjusted for the total amount of loop diuretics received, suggesting that adequacy of loop diuretic dosing to reach the 'ceiling' threshold is key[78]. The individual ceiling dose in each patient is difficult and can be influenced by many factors, such as non-naive with loop diuretics, body composition, the extent of volume overload and renal function. Nonetheless, intravenous doses

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ranging between 400–600 mg furosemide vs. 10–15 mg bumetanide is generally considered as the maximal total daily dose. When exceeded, additional natriuresis should be expected but this will lead to an increase in the side effects. Intravenous loop diuretics should be administered as soon as possible, since early loop diuretic administration is associated with lower in-hospital mortality[79]. In the DOSE-AHF trial, no difference was seen in the primary endpoint between continuous or bolus infusion. If bolus infusion is chosen, doses should be administered with at least 6 h intervals, to maximize the time above the natriuretic threshold and to avoid rebounding sodium retention[80].

Over the years many efforts were made to decrease both the resistance and the side effects of LD. Another well investigated approach is the one of changing the diuretic agent into torasemide.It is known to have the longest half-life at 3 to 4 hours and can be as long as 5 to 6 hours in patients with renal/hepatic dysfunction or heart failure. Bumetanide and torsemide, exhibit higher and more consistent oral bioavailability (>90%), and do not exhibit absorption-limited kinetics, making oral and intravenous doses more comparable.In a recent meta-analysis Miles et al. describe a reduction in intermediate-term heart failure readmissions and improvement in New York Heart Association class driven by torsemide compared with furosemide but is not associated with a reduced mortality risk[81]. TRANSFORM HF trial, recruited 2859 participants hospitalized with heart failure and compared directly the novel loop diuretic torsemide (n = 1431) with furosemide (n = 1428) with investigator-selected dosage. Among patients discharged after hospitalization for heart failure, torsemide compared with furosemide did not result in a significant difference in all-cause mortality over 12 months[82]. Similar results were seen also in the ASCEND-HF trial where furosemide was also compared with torasemide and showed that torsemide use was not associated with significantly improved outcomes. However, in this trial Patients receiving torsemide had more comorbidities than those receiving furosemide. The landmark study about torsemide is the TORIC study, which compared torsemide to furosemide and found that after an average of 9 months there was a significant 51.5% reduction in the risk of overall mortality, 59.7% reduction in cardiac mortality, as well as significant improvement in functional status within the torsemide group[83]. Unfortunately, the limitations put by the study design that did not proceed to randomization, the sample population which was mainly rural non-hospital based and the use of other standard HF-pharmacotherapies such as beta-blockers and ACE inhibitors was low (~9.5% and ~30%, respectively).

Mineralocortiocoid

Mineralocorticoid antagonists such as spironolactone improve mortality in heart failure with reduced ejection fraction but need to be used at low doses of 25 mg in order to avoid hyperkalemia. Several small studies suggested that when mineralocorticoid antagonists are given in higher doses, called “natriuretic doses”, might improve decongestion in ADHF[84]. The ATHENA study randomized 360 patients with ADHF and congestion to 96 hours of spironolactone (100mg daily) or placebo, but with low dose spironolactone continued[85]. Spironolactone did not improve either the primary endpoint of decongestion, measured by change in NT-proBNP or secondary endpoints, including symptoms amelioration and decongestion. In contrast to the anticipated increase in potassium levels, plasma potassium concentration was not affected, suggesting incomplete mineralocorticoid receptor blockade.

Carbonic Anhydrase Inhibitor

As described above, one of the targets in heart failure is sodium reabsorption in the proximal tubules. Firstly, in a state of decompensated heart failure, sodium is reabsorbed mostly in the proximal nephron. Secondly, greater delivery of chloride delivery to the macula densa cells increases, leading to decrease in renin production, which reduces neurohumoral activation.Third, endogenous natriuretic peptides will possibly regain their cardioprotective effects. The carbonic anhydrase inhibitor acetazolamide acts in the proximal tubules inhibiting sodium reabsorption. An observational study in patients with decompensated heart failure and significant fluid overload showed that adding acetazolamide (500 mg intravenous bolus on top of loop diuretic) improved loop diuretic response with approximately 100 mmol $Na^+$ excreted per 40 mg of furosemide dose

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equivalents[86] . This synergic effect of acetazolamide with loop diuretics was observed also in a small, randomized trial with 24 patients, presenting with acute fluid overload resistant to loop diuretic therapy[87]. A multicentre, randomized, double-blind, clinical trial of the diuretic effects of Acetazolamide in Decompensated heart failure with Volume OveRload (ADVOR) investigated whether acetazolamide can improve the efficiency of loop diuretics leading to faster and more efficient decongestion in ADHF. A total of 519 patients underwent randomization. 108 of 256 in the treatment arm (42.2%) were successfully decongested as compared with 79 out of 259 (30.5%) in the placebo group (risk ratio, 1.46;95% confidence interval [CI], 1.17 to 1.82; P<0.001). Death rate and rehospitalization rate was similar in both groups (29.7% vs 27.8%) The treatment group had higher urine output and natriuresis, presenting overall better diuretic effect. Adverse events, expressed by worsening kidney function, hypokalemia, and hypotension were similar in both groups[88].

SGLT2 Inhibitors

Sodium - glucose cotransporter 2 (SGLT2) inhibitors are the novel glucose lowering treatment that blocks the SGLT2 protein which is located in the proximal convoluted tubule of the nephron in the type 2 adult patients. The substances are canagliflozin, dapagliflozin and empagliflozin[89]. The Empagliflozin Outcome Event Trial in Type 2 Diabetes Mellitus Patients – Removing Excess Glucose (EMPA-REG OUTCOME) among patients with cardiovascular disease history, indicated a significant reduction in composite risk of cardiovascular death, myocardial infarction or stroke by 14%. Overall, the risk of all-cause mortality was reduced by 32% during a follow up period of 3.1 years[90]. Whether SGLT2 inhibitors provide clinical benefits in patients with AHF is being thoroughly explored. A total number of 1831 patients took part in three different trials with their baseline characteristics mostly similar between interventional and control groups. The drug of choice was Empagliflozin in EMPULSE[91] and EMPA - RESPONSE - WHF[92] and Sotagiflozin in SOLOIST - WHF[93]. Compared with the placebo group, the risk of mortality was reduced by 27% in the intervention group (RR: 0.73, 95% CI: 0.49–1.09, $p$ = 0.12, I2 = 18%). The mortality risk reduction was 15% in patients with Acute Decompensated Congestive Heart Failure (ADCHF) who took SGLT2 inhibitors compared to placebo (RR:0.85, 95% CI: 0.62–1.15, $p$ = 0.39, I2 = 0%). Compared to the placebo group, the intervention group had a significant risk reduction of 62% in Heart Failure Events (HFEs) (RR: 0.66, 95% CI: 0.58–0.75, $p$ < 0.0001, I2 = 0%), defined as a hospitalization or visits in the emergency department, or an outpatient visit necessitating intensification of treatment. Serious events were slightly lower in the intervention group by 15%, demonstrating favorable safety profile in the three SGLT2 trials in acute heart failure (RR: 0.85, 95% CI: 0.70–1.03, $p$ = 0.1, I2 = 44%). By the end of 2022, 15 clinical trials are being conducted testing the efficacy and safety of SGLT2 inhibitors on heart failure, diabetes mellitus type 2, acute myocardial infarction, and chronic kidney disease. The controlled substances are Empagliflozin of 10 and 20 mg, Dapagliflozin of 10 mg and Canagliflozin. Control and group standard care consist of either placebo or loop diuretics, vasodilators, inotropic agents, digoxin, and/or vasopressors.

Miscellaneous approaches (oral vasopressin-2 receptor antagonist, hypertonic solutions, dopamine)

Hyponatremia, reflecting water accumulation, is common in heart failure patients and is a poor prognostic indicator[94]. The oral vasopressin-2 receptor antagonist tolvaptan inhibits the action of antidiuretic hormone and increases free water excretion[95]. The EVEREST study, that evaluated hospitalized heart failure patients (with or without hyponatremia), did not demonstrate superiority of tolvaptan over placebo in terms of long-term clinical outcomes. However, a beneficial effect on volume status and symptoms was observed in the initial treatment days[96]. Smaller trials focused on tolvaptan use in patients with lower serum sodium levels to achieve short term decongestion, did not show significant improvement in symptoms or clinical outcomes, despite leading to greater weight and fluid loss[97].

A randomized, single-blind study evaluated the effects of the combination of high-dose furosemide and small-volume hypertonic saline solution (HSS) infusion in the treatment of refractory New York Heart Association (NYHA) class IV CHF and a normal sodium diet during follow-up[98]. Patients were randomized into 2 groups. Patients in group 1 received an intravenous (IV) infusion of

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furosemide (500-1000 mg) plus HSS twice a day for 30 minutes. Patients in group 2 received an IV bolus of furosemide (500-1000 mg) twice a day, without HSS, during a period lasting 6 to 12 days. The results showed an improvement in quality of life, a delay in upscaling diuretic treatment and a trend towards decreasing mortality.

When renal blood flow decreases, it contributes to sodium retention in ADHF. The proposed mechanism is the limited Na+ filtration, increased Na+ reabsorption, and reduced renal diuretic delivery to the proximal tubule. Dopamine increases renal blood flow and was shown to cause urinary Na+ excretion at low doses[99] and therefore enhances natriuresis. The ROSE-AHF study randomized 360 patients hospitalized for ADHF with impaired renal function to furosemide plus either dopamine infusion (2 μg/kg/min), nesiritide (0.005 μg/kg/min), or placebo[100]. Urine volume or changes in cystatin C level for 72 hours were not affected by the two drugs. Dopamine infusion was associated with tachycardia (7% for dopamine vs. 1% for placebo, $p > 0.001$), even in this low dose. A post hoc subgroup analysis suggested that low dose dopamine effect could be different according to the heart failure subtype; in patients with heart failure with reduced ejection fraction (HFrEF) dopamine may improve decongestion and prognosis[101].

**4. Ultrafiltration Strategy (UF)**

For years the concept of a rapid decongestant done mechanically by an ultrafiltration (UF) device has been under thorough investigation. UF presents many advantages over the classic diuretic treatment. These consist of precise control of rate and amount of fluid removal, restoration of fluid responsiveness, removal of isotonic plasma water, no effect on plasma concentration of potassium and magnesium and finally it does not exert direct neurohormonal activation. The disadvantages of the method are the need for anticoagulation, the need for a peripheral or central venous catheter and the need for extracorporeal circuit[102]. UNLOAD, CARRESS-HF, CUORE, AVOID-HF, are trials that investigated the role of UF in Acutely Decompensated Congestive Heart Failure (ADCHF). The key lessons from these trials are that UF can restore diuretic agent responsiveness, but overly aggressive fluid removal can convert nonoliguric renal dysfunction into oliguric failure and dialysis dependence.

The UNLOAD (UF Versus IV Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure, n=200) trial[103] was a multicenter, single session, UF therapy for ADHF within 24 hours. The trial showed that, compared with patients receiving intravenous (iv) Loop Diuretics (LD), those randomized to the ultrafiltration arm had greater weight and net fluid loss at 48 hours and a 53% reduction in the 90 – day risk of hospitalization and unscheduled visits for heart failure (p=0.0037). In decompensated HF, UF can safely produce weight and fluid loss than iv diuretics, reduces 90-day resource utilization for HF and is an effective alternative therapy.

In contrast to the results of the UNLOAD trial, which tested the effects of early decongestive strategies, the CARRESS – HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure, n=188) trial[104] showed that a stepped pharmacologic therapy algorithm was both superior and safer than a fixed 200ml/h UF rate for the preservation of renal function at 96 hours. The use of diuretics was superior to a strategy of UF for the preservation of renal function at 96 hours, with a similar amount of weight loss on the two approaches. UF was associated with a higher rate of adverse events.

The AVOID – HF (Aquapheresis Versus IV Diuretics and Hospitalization for HF, n=227) trial[105] showed that the Adjustable Ultrafiltration (AUF) group, compared with the Adjustable Loop Diuretic (ALD) group had a non – statistically significant trend toward a longer time to first HF event after index hospitalization, significantly fewer patients rehospitalized and with shorter hospitalization time for HF or CV causes at 30 days. Whereas 90 – day mortality did not differ between groups, the number of patients experiencing an adverse event of special interest, or a serious product related side effect was greater in the AUF than in the ALD group. The study was prematurely terminated by the sponsor. Nevertheless, the results of the AVOID – HF trial suggest that decongestion with UF requires careful evaluation of the benefit of reducing HF rehospitalizations with the risk of UF – related adverse events.

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The CUORE trial[106], a small (n=56), prospective, randomized, unblinded study compared ultrafiltration and standard medical treatment. It did not include patients with acutely decompensated heart failure or cardiogenic shock. Moreover, the randomization took place 24 hours post admission and the fluid removal could not exceed 75% of the estimated initial weight increase. The intravenous dosage of diuretics that started before randomization was left unchanged in both groups.

## 5. Guidelines

According to the ESC guidelines for heart failure diuretics are recommended in patients with congestion and both HFrEF and HFmrEF, with a class I level C recommendation, in order to alleviate symptoms and signs. UF still searches its place in HF patients, as it is recommended in patients with advanced HF when in refractory volume overload, which is unresponsive to diuretic treatment with a class IIb indication level C. Renal replacement therapy should be considered in patients with refractory volume overload and end-stage kidney failure with a class IIa recommendation level C[11].

## 6. Conclusions

Multiple factors can contribute to the accumulation and redistribution of body fluid to the interstitial and intravascular compartments often leading to volume overload and organ congestion.The renal retention of sodium and water is an early response mechanism contributing to fluid accumulation. The skillful use of diuretic therapy remains fundamental to HF management. The optimal assessment of volume status in HF patients is vital particularly during the early management of the disease. LD is frequently used as the initial therapy to treat HF patients with fluid overload. Unfortunately, diuretics can have limited effectiveness due to several factors such as underlying acute kidney injury that contribute to diuretic resistance. UF and renal replacement therapies are often required for optimal volume management in patients with fluid overload, as a bail-out treatment. It is of paramount importance to successfully estimate patients' fluid status and set clear treatment goals. These goals seem to be achieved faster and more efficiently by ultrafiltration.

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## References

1. Crespo-Leiro, M. G., Anker, S. D., Maggioni, A. P., Coats, A. J., Filippatos, G., Ruschitzka, F., Ferrari, R., Piepoli, M. F., Delgado Jimenez, J. F., Metra, M., Fonseca, C., Hradec, J., Amir, O., Logeart, D., Dahlström, U., Merkely, B., Drozdz, J., Goncalvesova, E., Hassanein, M., … (ESC), on behalf of the H. F. A. (HFA) of the E. S. of C. (2016). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. European Journal of Heart Failure, 18(6), 613–625. https://doi.org/https://doi.org/10.1002/ejhf.566.
2. Hernandez AF, Greiner MA, Fonarow GC; et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. JAMA. 2010;303(17):1716-1722. https://doi.org/10.1001/jama.2010.533.
3. Setoguchi, S., Stevenson, L. W., & Schneeweiss, S. (2007). Repeated hospitalizations predict mortality in the community population with heart failure. American Heart Journal, 154(2), 260–266. https://doi.org/10.1016/J.AHJ.2007.01.041.
4. Verbrugge, F. H., Dupont, M., Steels, P., Grieten, L., Swennen, Q., Tang, W. H. W., & Mullens, W. (2014). The kidney in congestive heart failure: "are natriuresis, sodium, and diuretics really the good, the bad and the ugly?" European Journal of Heart Failure, 16(2), 133–142. https://doi.org/10.1002/EJHF.35.
5. Braam, B., Cupples, W. A., Joles, J. A., & Gaillard, C. (2012). Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. Heart Failure Reviews, 17(2), 161–175. https://doi.org/10.1007/S10741-011-9246-2.

6. Colombo, P. C., Onat, D., Harxhi, A., Demmer, R. T., Hayashi, Y., Jelic, S., Lejemtel, T. H., Bucciarelli, L., Kebschull, M., Papapanou, P., Uriel, N., Schmidt, A. M., Sabbah, H. N., & Jorde, U. P. (2014). Peripheral venous congestion causes inflammation, neurohormonal, and endothelial cell activation. European Heart Journal, 35(7), 448–454. https://doi.org/10.1093/EURHEARTJ/EHT456.
7. Metra, M., Davison, B., Bettari, L., Sun, H., Edwards, C., Lazzarini, V., Piovanelli, B., Carubelli, V., Bugatti, S., Lombardi, C., Cotter, G., & Dei Cas, L. (2012). Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circulation. Heart Failure, 5(1), 54–62. https://doi.org/10.1161/CIRCHEARTFAILURE.111.963413.
8. Rosano GMC, Moura B, Metra M; et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2021;23(6):872-881. https://doi.org/10.1002/ejhf.2206.
9. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016;13(6):368-378. https://doi.org/10.1038/nrcardio.2016.25.
10. Lind L, Ingelsson M, Sundstrom J, Ärnlöv J. Impact of risk factors for major cardiovascular diseases: A comparison of life-time observational and Mendelian randomisation findings. Open Heart. 2021;8(2):e001735. https://doi.org/10.1136/openhrt-2021-001735.
11. McDonagh TA, Metra M, Adamo M; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in Eur Heart J. 2021 Oct 14;:]. Eur Heart J. 2021;42(36):3599-3726. https://doi.org/10.1093/eurheartj/ehab368.
12. SKINNER, S. L., MCCUBBIN, J. W., & PAGE, I. H. (1964). Renal Baroreceptor Control of Acute Renin Release in Normotensive, Nephrogenic and Neurogenic Hypertensive Dogs. Circulation Research, 15, 522–531. https://doi.org/10.1161/01.RES.15.6.522.
13. Clark AL, Cleland JG. Causes and treatment of oedema in patients with heart failure. Nat Rev Cardiol. 2013;10(3):156-170. https://doi.org/10.1038/nrcardio.2012.191.
14. Fallick, C., Sobotka, P. A., & Dunlap, M. E. (2011). Sympathetically Mediated Changes in Capacitance. Circulation: Heart Failure, 4(5), 669–675. https://doi.org/10.1161/CIRCHEARTFAILURE.111.961789.
15. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovasc Pathol. 2012;21(5):365-371. https://doi.org/10.1016/j.carpath.2011.11.007.
16. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316(23):1429-1435. https://doi.org/10.1056/NEJM198706043162301.
17. Salahuddin, N., Sammani, M., Hamdan, A., Joseph, M., Al-Nemary, Y., Alquaiz, R., Dahli, R., & Maghrabi, K. (2017). Fluid overload is an independent risk factor for acute kidney injury in critically Ill patients: Results of a cohort study. BMC Nephrology, 18(1), 1–8. https://doi.org/10.1186/S12882-017-0460-6/TABLES/2.
18. Patil VP, Salunke BG. Fluid Overload and Acute Kidney Injury. Indian J Crit Care Med. 2020;24(Suppl 3):S94-S97. https://doi.org/10.5005/jp-journals-10071-23401.
19. Urso C, Brucculeri S, Caimi G. Acid-base and electrolyte abnormalities in heart failure: Pathophysiology and implications. Heart Fail Rev. 2015;20(4):493-503. https://doi.org/10.1007/s10741-015-9482-y.
20. Elisaf MS, Siamopoulos KC. Acid–base and electrolyte abnormalities in patients with congestive heart failure. Exp Clin Cardiol. 1997;2:140–144.
21. Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342(21):1581-1589. https://doi.org/10.1056/NEJM200005253422107.
22. Filippatos TD, Elisaf MS. Hyponatremia in patients with heart failure. World J Cardiol. 2013 Sep 26;5(9):317-28. https://doi.org/10.4330/wjc.v5.i9.317. PMID: 24109495; PMCID: PMC3783984.
23. Klein L, O'Connor CM, Leimberger JD; et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: Results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. Circulation. 2005;111(19):2454-2460. https://doi.org/10.1161/01.CIR.0000165065.82609.3D.
24. Cleland JG, Dargie HJ, Robertson I, Robertson JI, East BW. Total body electrolyte composition in patients with heart failure: A comparison with normal subjects and patients with untreated hypertension. Br Heart J. 1987 Sep;58(3):230-8. https://doi.org/10.1136/hrt.58.3.230. PMID: 3311097; PMCID: PMC1216442.
25. Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients?. J Am Coll Cardiol. 2004;43(2):155-161. https://doi.org/10.1016/j.jacc.2003.06.021.
26. Packer M. Potential role of potassium as a determinant of morbidity and mortality in patients with systemic hypertension and congestive heart failure. Am J Cardiol. 1990;65(10):45E-52E. https://doi.org/10.1016/0002-9149(90)90251-u.
27. Williams, G. H. (2005). Aldosterone and heart failure: The rest of the story. Heart Failure Reviews, 10(1), 5–6. https://doi.org/10.1007/S10741-005-2342-4/METRICS.
28. Bielecka-Dabrowa A, Mikhailidis DP, Jones L, Rysz J, Aronow WS, Banach M. The meaning of hypokalemia in heart failure. Int J Cardiol. 2012;158(1):12-17. https://doi.org/10.1016/j.ijcard.2011.06.121.

29. Ralston, M. A., Murnane, M. R., Unverferth, D. v., & Leier, C. v. (1990). Serum and tissue magnesium concentrations in patients with heart failure and serious ventricular arrhythmias. Annals of Internal Medicine, 113(11), 841–846. https://doi.org/10.7326/0003-4819-113-11-841.
30. Seelig, M.S., and Haddy, F.J. Magnesium and the arteries. I. Effects of magnesium on arteries and on the retention of sodium, potassium, and calcium, in Magnesium in Health and Disease. Proceedings of the Second International Symposium on Magnesium, American College of Nutrition, Society for Development of Research in Magnesium, University of Montreal, Montreal, Canada, 1976. M. Cantin and M.S. Seelig, eds. SP Medical & Scientific Books, Jamaica, N.Y. (1980), pp. 605–638.
31. Douban S, Brodsky MA, Whang DD, Whang R. Significance of magnesium in congestive heart failure. Am Heart J. 1996;132(3):664-671. https://doi.org/10.1016/s0002-8703(96)90253-7.
32. Wester, P. O. (1992). Electrolyte balance in heart failure and the role of magnesium ions. The American Journal of Cardiology, 70(10), 44–49. https://doi.org/10.1016/0002-9149(92)91357-A.
33. Bourdeau, J., Buss, S., and, G. V.-J. of P., & 1982, undefined. (n.d.). Inhibition of calcium absorption in the cortical thick ascending limb of Henle's loop by furosemide. https://jpet.aspetjournals.org/content/221/3/815.short.
34. Rimailho A, Bouchard P, Schaison G, Richard C, Auzépy P. Improvement of hypocalcemic cardiomyopathy by correction of serum calcium level. Am Heart J. 1985;109(3 Pt 1):611-613. https://doi.org/10.1016/0002-8703(85)90579-4.
35. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: Problems and perspectives. J Am Coll Cardiol. 2013;61(4):391-403. https://doi.org/10.1016/j.jacc.2012.09.038.
36. Clin. Cardiol. 32, 2, 67–68 (2009)Roger M. Mills et al.: The Heart Failure Frequent Flyer: An Urban LegendPublished online in Wiley InterScience. (www.interscience.wiley.com)DOI:10.1002/clc.204042009 Wiley Periodicals, Inc.
37. Koratala A, Kazory A. Natriuretic Peptides as Biomarkers for Congestive States: The Cardiorenal Divergence. Dis Markers. 2017;2017:1454986. https://doi.org/10.1155/2017/1454986.
38. Boyle A, Sobotka PA. Redefining the therapeutic objective in decompensated heart failure: Hemoconcentration as a surrogate for plasma refill rate. J Card Fail. 2006;12(4):247-249. https://doi.org/10.1016/j.cardfail.2006.01.011.
39. Fujita T, Inomata T, Yazaki M; et al. Hemodilution after Initial Treatment in Patients with Acute Decompensated Heart Failure. Int Heart J. 2018;59(3):573-579. https://doi.org/10.1536/ihj.17-307.
40. van der Meer P, Postmus D, Ponikowski P; et al. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. J Am Coll Cardiol. 2013;61(19):1973-1981. https://doi.org/10.1016/j.jacc.2012.12.050.
41. Sharma R, Francis DP, Pitt B, Poole-Wilson PA, Coats AJ, Anker SD. Haemoglobin predicts survival in patients with chronic heart failure: A substudy of the ELITE II trial. Eur Heart J. 2004;25(12):1021-1028. https://doi.org/10.1016/j.ehj.2004.04.023.
42. Denault AY, Langevin S, Lessard MR, Courval JF, Desjardins G. Transthoracic echocardiographic evaluation of the heart and great vessels. Évaluation échocardiographique transthoracique du cœur et des grands vaisseaux. Can J Anaesth. 2018;65(4):449-472. https://doi.org/10.1007/s12630-018-1068-4.
43. Konstam MA, Kiernan MS, Bernstein D; et al. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2018;137(20):e578-e622. https://doi.org/10.1161/CIR.0000000000000560.
44. Rudski LG, Lai WW, Afilalo J; et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23(7):685-788. https://doi.org/10.1016/j.echo.2010.05.010.
45. Greenway CV, Lautt WW. Distensibility of hepatic venous resistance sites and consequences on portal pressure. Am J Physiol. 1988;254(3 Pt 2):H452-H458. https://doi.org/10.1152/ajpheart.1988.254.3.H452.
46. Beaubien-Souligny W, Rhéaume M, Blondin MC; et al. A Simplified Approach to Extravascular Lung Water Assessment Using Point-of-Care Ultrasound in Patients with End-Stage Chronic Renal Failure Undergoing Hemodialysis. Blood Purif. 2018;45(1-3):79-87. https://doi.org/10.1159/000481768.
47. Singh NG, Kumar KN, Nagaraja PS, Manjunatha N. Portal venous pulsatility fraction, a novel transesophageal echocardiographic marker for right ventricular dysfunction in cardiac surgical patients. Ann Card Anaesth. 2020;23(1):39-42. https://doi.org/10.4103/aca.ACA_250_18.
48. Eljaiek R, Cavayas YA, Rodrigue E; et al. High postoperative portal venous flow pulsatility indicates right ventricular dysfunction and predicts complications in cardiac surgery patients. Br J Anaesth. 2019;122(2):206-214. https://doi.org/10.1016/j.bja.2018.09.028.
49. Collins SP, Lindsell CJ, Storrow AB, Abraham WT; ADHERE Scientific Advisory Committee, Investigators and Study Group. Prevalence of negative chest radiography results in the emergency department patient with decompensated heart failure. Ann Emerg Med. 2006;47(1):13-18. https://doi.org/10.1016/j.annemergmed.2005.04.003.

50. Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: A systematic review. Eur J Heart Fail. 2017;19(9):1154-1163. https://doi.org/10.1002/ejhf.839.
51. Shankar SS, Brater DC. Loop diuretics: From the Na-K-2Cl transporter to clinical use. Am J Physiol Renal Physiol. 2003;284(1):F11-F21. https://doi.org/10.1152/ajprenal.00119.2002.
52. Gottlieb SS, Khatta M, Wentworth D, Roffman D, Fisher ML, Kramer WG. The effects of diuresis on the pharmacokinetics of the loop diuretics furosemide and torsemide in patients with heart failure. Am J Med. 1998;104(6):533-538. https://doi.org/10.1016/s0002-9343(98)00111-9.
53. McCrindle JL, Li Kam Wa TC, Barron W, Prescott LF. Effect of food on the absorption of frusemide and bumetanide in man. Br J Clin Pharmacol. 1996;42(6):743-746. https://doi.org/10.1046/j.1365-2125.1996.00494.x.
54. Dennis L. Vargo MD, William G. Kramer PhD, Paula K. Black RN, William B. Smith MD, Tina Serpas RN, D. Craig Brater MD. Clinical pharmacology and therapeutics. 1995;57:601–609.
55. Vasko, M. R., Cartwright, D. B., Knochel, J. P., Nixon, J. v., & Brater, D. C. (1985). Furosemide absorption altered in decompensated congestive heart failure. Annals of Internal Medicine, 102(3), 314–318. https://doi.org/10.7326/0003-4819-102-3-314.
56. Ferrari, R., Balla, C., & Fucili, A. (2016). Heart failure: An historical perspective. European Heart Journal Supplements, 18(suppl_G), G3–G10. https://doi.org/10.1093/EURHEARTJ/SUW042.
57. Bianucci R, Loynes RD, Sutherland ML; et al. Forensic Analysis Reveals Acute Decompensation of Chronic Heart Failure in a 3500-Year-Old Egyptian Dignitary. J Forensic Sci. 2016;61(5):1378-1381. https://doi.org/10.1111/1556-4029.13138.
58. Katz AM. The "modern" view of heart failure: How did we get here?. Circ Heart Fail. 2008;1(1):63-71. https://doi.org/10.1161/CIRCHEARTFAILURE.108.772756.
59. The Linacre Lecture on the Law of the Heart Given at Cambridge, 1915. (1918). Nature 1918 101:2525, 101(2525), 43–43. https://doi.org/10.1038/101043a0.
60. Anand, I. S., Ferrari, R., Kalra, G. S., Wahi, P. L., Poole-Wilson, P. A., & Harris, P. C. (1991). Pathogenesis of edema in constrictive pericarditis. Studies of body water and sodium, renal function, hemodynamics, and plasma hormones before and after pericardiectomy. Circulation, 83(6), 1880–1887. https://doi.org/10.1161/01.CIR.83.6.1880.
61. Rangaswami, J., Bhalla, V., Blair, J. E. A., Chang, T. I., Costa, S., Lentine, K. L., Lerma, E. v., Mezue, K., Molitch, M., Mullens, W., Ronco, C., Tang, W. H. W., & Mccullough, P. A. (2019). Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Circulation, 139(16), E840–E878. https://doi.org/10.1161/CIR.0000000000000664.
62. Jentzer JC, Bihorac A, Brusca SB; et al. Contemporary Management of Severe Acute Kidney Injury and Refractory Cardiorenal Syndrome: JACC Council Perspectives [published correction appears in J Am Coll Cardiol. 2021 Jan 5;77(1):107-109]. J Am Coll Cardiol. 2020;76(9):1084-1101. https://doi.org/10.1016/j.jacc.2020.06.070.
63. Felker, G. M., Ellison, D. H., Mullens, W., Cox, Z. L., & Testani, J. M. (2020). Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. Journal of the American College of Cardiology, 75(10), 1178–1195. https://doi.org/10.1016/J.JACC.2019.12.059.
64. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA. Diuretic response in acute heart failure-pathophysiology, evaluation, and therapy. Nat Rev Cardiol. 2015;12(3):184-192. https://doi.org/10.1038/nrcardio.2014.215.
65. Neuberg GW, Miller AB, O'Connor CM; et al. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J. 2002;144(1):31-38. https://doi.org/10.1067/mhj.2002.123144.
66. Wilcox CS, Mitch WE, Kelly RA; et al. Response of the kidney to furosemide. I. Effects of salt intake and renal compensation. J Lab Clin Med. 1983;102(3):450-458.
67. Testani JM, Brisco MA, Turner JM; et al. Loop diuretic efficiency: A metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail. 2014;7(2):261-270. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000895.
68. Vargo DL, Kramer WG, Black PK, Smith WB, Serpas T, Brater DC. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. Clin Pharmacol Ther. 1995;57(6):601-609. https://doi.org/10.1016/0009-9236(95)90222-8.
69. Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(10):1178-1195. https://doi.org/10.1016/j.jacc.2019.12.059.
70. Gheorghiade, M., & Filippatos, G. (2005). Reassessing treatment of acute heart failure syndromes: The ADHERE Registry. European Heart Journal Supplements, 7(suppl_B), B13–B19. https://doi.org/10.1093/EURHEARTJ/SUI008.

71. Felker GM, Lee KL, Bull DA; et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797-805. https://doi.org/10.1056/NEJMoa1005419.
72. Testani JM, Brisco MA, Kociol RD; et al. Substantial Discrepancy Between Fluid and Weight Loss During Acute Decompensated Heart Failure Treatment. Am J Med. 2015;128(7):776-83.e4. https://doi.org/10.1016/j.amjmed.2014.12.020.
73. Testani JM, Hanberg JS, Cheng S; et al. Rapid and Highly Accurate Prediction of Poor Loop Diuretic Natriuretic Response in Patients With Heart Failure. Circ Heart Fail. 2016;9(1):e002370. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002370.
74. Testani JM, Brisco MA, Turner JM; et al. Loop diuretic efficiency: A metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail. 2014;7(2):261-270. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000895.
75. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol. 2010;56(19):1527-1534. https://doi.org/10.1016/j.jacc.2010.06.034.
76. Agarwal R, Sinha AD. Thiazide diuretics in advanced chronic kidney disease. J Am Soc Hypertens. 2012;6(5):299-308. https://doi.org/10.1016/j.jash.2012.07.004.
77. Brisco MA, Zile MR, Hanberg JS; et al. Relevance of Changes in Serum Creatinine During a Heart Failure Trial of Decongestive Strategies: Insights From the DOSE Trial. J Card Fail. 2016;22(10):753-760. https://doi.org/10.1016/j.cardfail.2016.06.423.
78. Hanberg JS, Tang WHW, Wilson FP; et al. An exploratory analysis of the competing effects of aggressive decongestion and high-dose loop diuretic therapy in the DOSE trial. Int J Cardiol. 2017;241:277-282. https://doi.org/10.1016/j.ijcard.2017.03.114.
79. Matsue Y, Damman K, Voors AA; et al. Time-to-Furosemide Treatment and Mortality in Patients Hospitalized With Acute Heart Failure. J Am Coll Cardiol. 2017;69(25):3042-3051. https://doi.org/10.1016/j.jacc.2017.04.042.
80. Heart Failure Society of America, Lindenfeld J, Albert NM; et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010;16(6):e1-e194. https://doi.org/10.1016/j.cardfail.2010.04.004.
81. Miles JA, Hanumanthu BK, Patel K, Chen M, Siegel RM, Kokkinidis DG. Torsemide versus furosemide and intermediate-term outcomes in patients with heart failure: An updated meta-analysis. J Cardiovasc Med (Hagerstown). 2019;20(6):379-388. https://doi.org/10.2459/JCM.0000000000000794.
82. Mentz RJ, Anstrom KJ, Eisenstein EL; et al. Effect of Torsemide vs Furosemide After Discharge on All-Cause Mortality in Patients Hospitalized With Heart Failure: The TRANSFORM-HF Randomized Clinical Trial. JAMA. 2023;329(3):214-223. https://doi.org/10.1001/jama.2022.23924.
83. Cosín J, Díez J; TORIC investigators. Torasemide in chronic heart failure: Results of the TORIC study [published correction appears in Eur J Heart Fail 2002 Oct;4(5):667]. Eur J Heart Fail. 2002;4(4):507-513. https://doi.org/10.1016/s1388-9842(02)00122-8.
84. Eng M, Bansal S. Use of natriuretic-doses of spironolactone for treatment of loop diuretic resistant acute decompensated heart failure. Int J Cardiol. 2014;170(3):e68-e69. https://doi.org/10.1016/j.ijcard.2013.11.023.
85. 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(9):950-958. https://doi.org/10.1001/jamacardio.2017.2198.
86. Verbrugge FH, Dupont M, Bertrand PB; et al. Determinants and impact of the natriuretic response to diuretic therapy in heart failure with reduced ejection fraction and volume overload. *Acta Cardiol*. 2015;70(3):265-273. https://doi.org/10.1080/ac.70.3.3080630.
87. Knauf H, Mutschler E. Sequential nephron blockade breaks resistance to diuretics in edematous states. *J Cardiovasc Pharmacol*. 1997;29(3):367-372. https://doi.org/10.1097/00005344-199703000-00010.
88. Mullens, W., Dauw, J., Martens, P., Verbrugge, F. H., Nijst, P., Meekers, E., Tartaglia, K., Chenot, F., Moubayed, S., Dierckx, R., Blouard, P., Troisfontaines, P., Derthoo, D., Smolders, W., Bruckers, L., Droogne, W., ter Maaten, J. M., Damman, K., Lassus, J., … Dupont, M. (2022). Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. *New England Journal of Medicine*, *387*(13), 1185–1195. https://doi.org/10.1056/NEJMOA2203094/SUPPL_FILE/NEJMOA2203094_DATA-SHARING.PDF.
89. Boorsma EM, Beusekamp JC, Ter Maaten JM; et al. Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. *Eur J Heart Fail*. 2021;23(1):68-78. https://doi.org/10.1002/ejhf.2066.
90. Savarese G, Sattar N, Januzzi J; et al. Empagliflozin Is Associated With a Lower Risk of Post-Acute Heart Failure Rehospitalization and Mortality. *Circulation*. 2019;139(11):1458-1460. https://doi.org/10.1161/CIRCULATIONAHA.118.038339.
91. Voors AA, Angermann CE, Teerlink JR; et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: A multinational randomized trial. *Nat Med*. 2022;28(3):568-574. https://doi.org/10.1038/s41591-021-01659-1.

92. Damman K, Beusekamp JC, Boorsma EM; et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail*. 2020;22(4):713-722. https://doi.org/10.1002/ejhf.1713.
93. Bhatt DL, Szarek M, Steg PG; et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021;384(2):117-128. https://doi.org/10.1056/NEJMoa2030183.
94. Members, A. F., McMurray, J. J. V., Adamopoulos, S., Anker, S. D., Auricchio, A., Böhm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C., Gomez-Sanchez, M. A., Jaarsma, T., Køber, L., Lip, G. Y. H., Maggioni, A. pietro, Parkhomenko, A., Pieske, B. M., Popescu, B. A., Rønnevik, P. K., … Ponikowski, P. (2012). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal, 33(14), 1787–1847. https://doi.org/10.1093/EURHEARTJ/EHS104.
95. Gheorghiade M, Gattis WA, O'Connor CM; et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. JAMA. 2004;291(16):1963-1971. https://doi.org/10.1001/jama.291.16.1963.
96. Pang PS, Konstam MA, Krasa HB; et al. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. Eur Heart J. 2009;30(18):2233-2240. https://doi.org/10.1093/eurheartj/ehp253.
97. Felker GM, Mentz RJ, Cole RT; et al. Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure. J Am Coll Cardiol. 2017;69(11):1399-1406. https://doi.org/10.1016/j.jacc.2016.09.004.
98. Licata G, Di Pasquale P, Parrinello G; et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: Long-term effects. Am Heart J. 2003;145(3):459-466. https://doi.org/10.1067/mhj.2003.166.
99. Ungar A, Fumagalli S, Marini M; et al. Renal, but not systemic, hemodynamic effects of dopamine are influenced by the severity of congestive heart failure. Crit Care Med. 2004;32(5):1125-1129. https://doi.org/10.1097/01.ccm.0000124871.58281.d1.
100. Chen HH, Anstrom KJ, Givertz MM; et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: The ROSE acute heart failure randomized trial. JAMA. 2013;310(23):2533-2543. https://doi.org/10.1001/jama.2013.282190.
101. Wan, S. H., Stevens, S. R., Borlaug, B. A., Anstrom, K. J., Deswal, A., Felker, G. M., Givertz, M. M., Bart, B. A., Tang, W. H. W., Redfield, M. M., & Chen, H. H. (2016). Differential response to low-dose dopamine or low-dose nesiritide in acute heart failure with reduced or preserved ejection fraction. Circulation: Heart Failure, 9(8). https://doi.org/10.1161/CIRCHEARTFAILURE.115.002593.
102. Costanzo MR, Ronco C, Abraham WT; et al. Extracorporeal Ultrafiltration for Fluid Overload in Heart Failure: Current Status and Prospects for Further Research. J Am Coll Cardiol. 2017;69(19):2428-2445. https://doi.org/10.1016/j.jacc.2017.03.528.
103. Costanzo MR, Guglin ME, Saltzberg MT; et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure [published correction appears in J Am Coll Cardiol. 2007 Mar 13;49(10):1136]. J Am Coll Cardiol. 2007;49(6):675-683. https://doi.org/10.1016/j.jacc.2006.07.073.
104. Grodin JL, Carter S, Bart BA, Goldsmith SR, Drazner MH, Tang WHW. Direct comparison of ultrafiltration to pharmacological decongestion in heart failure: A per-protocol analysis of CARRESS-HF. Eur J Heart Fail. 2018;20(7):1148-1156. https://doi.org/10.1002/ejhf.1158.
105. Costanzo MR, Negoianu D, Fonarow GC; et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. Am Heart J. 2015;170(3):471-482. https://doi.org/10.1016/j.ahj.2015.05.019.
106. Marenzi G, Muratori M, Cosentino ER; et al. Continuous ultrafiltration for congestive heart failure: The CUORE trial [published correction appears in J Card Fail. 2014 May;20(5):378]. J Card Fail. 2014;20(1):9-17. https://doi.org/10.1016/j.cardfail.2013.11.004.