Expert Opinion

Diuretics in clinical practice. Part I: mechanisms of action, pharmacological effects and clinical indications of diuretic compounds

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Importance of the field: Diuretics are among the most important drugs of our therapeutic armamentarium and have been broadly used for >50 years, providing important help towards the treatment of several diseases. Although all diuretics act primarily by impairing sodium reabsorption in the renal tubules, they differ in their mechanism and site of action and, therefore, in their specific pharmacological properties and clinical indications. Loop diuretics are mainly used for oedematous disorders (i.e., cardiac failure, nephrotic syndrome) and for blood pressure and volume control in renal disease; thiazides and related agents are among the most prescribed drugs for hypertension treatment; aldosterone-blockers are traditionally used for primary or secondary aldosteronism; and other diuretic classes have more specific indications.

Areas covered in this review: This article discusses the mechanisms of action, pharmacological effects and clinical indications of the various diuretic classes used in everyday clinical practice, with emphasis on recent knowledge suggesting beneficial effects of certain diuretics on clinical conditions distinct from the traditional indications of these drugs (i.e., heart protection for aldosterone blockers).

What the reader will gain: Reader will gain insights into the effective use of diuretic agents for various medical conditions, representing their established or emerging therapeutic indications.

Take home message: Knowledge of the pharmacologic properties and mechanisms of action of diuretic agents is a prerequisite for the successful choice and effective clinical use of these compounds.

Keywords: diuretics, loop diuretics, potassium-sparing diuretics, thiazides

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1. Introduction

The diuretic compounds are therapeutic tools used extensively and successfully for the treatment of various medical disorders all over the world. All diuretic agents act primarily by impairing Na^+ reabsorption in the renal tubules. However, they differ considerably in their chemical derivation and mechanism of action, that is, the specific tubular ion transport systems they interfere with. The latter determines the site of action along the nephron where each class of diuretics acts and, because physiologically the amount of Na^+ reabsorbed differs between the various segments of the nephron, it further determines the natriuretic efficacy, pharmacological effects and specific clinical indications of each diuretic [1,2]. Thus, knowledge of the

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Article highlights.

- All diuretic agents act primarily by impairing Na^+ reabsorption in the renal tubules; the site of action along the nephron where each class of diuretics acts determines the natriuretic efficacy, pharmacological effects and specific clinical indications of each diuretic.
- Carbonic anhydrase inhibitors interfere with the function of carbonic anhydrase within the brush border and inside the epithelial cells of the proximal tubule and their main clinical indication is treatment of glaucoma.
- Mannitol exerts an osmotic effect along the renal tubule, inhibiting water and solute reabsorption without interfering with tubular electrolyte transport systems and is widely used for treatment of cerebral oedema.
- Loop diuretics inhibit the Na^+-K^+-$2Cl^-$ co-transporter at the thick ascending limb of the loop of Henle and are successfully used in patients with oedematous disorders as well as for volume and blood pressure control in patients with chronic kidney disease. With regards to pharmacokinetics, furosemide, the most commonly used loop diuretic, is characterised by a short half-life and problematic bioavailability; thus, appropriate daily dosing of furosemide is required in order to achieve long-acting natriuretic efficacy.
- Thiazides and related agents inhibit an electroneutral NaCl co-transport pathway at the distal convoluted tubule and represent the cornerstone of antihypertensive therapy for many years; however, their natriuretic efficacy is significantly reduced in patients with glomerular filtration rate < 40 ml/min/1.73 m^2.
- Amiloride and triamterene inhibit the epithelial Na^+ channel of the collecting duct and are mainly used in the treatment of hypertension in combination with other diuretics to correct potassium deficiency in patients without mineralocorticoid excess.
- Spironolactone and eplerenone block the aldosterone mineralocorticoid receptors in the cytoplasm of principal cells of the collecting duct. Aldosterone antagonists are traditionally used for primary aldosteronism, but recent evidence indicates that they reduce morbidity and mortality in patients with heart failure.

This box summarises key points contained in the article.

pharmacology of diuretic agents, on one hand, and understanding of the pathophysiology of the patient's disease, on the other, are prerequisites for the successful choice and effective clinical use of a diuretic compound.

Due to the differences in pharmacology, the various diuretic classes have been differently used for common and less common medical conditions. Loop diuretics are usually the first choice for oedematous disorders (cardiac failure, nephrotic syndrome, hepatic cirrhosis), as well as for blood pressure (BP) and volume control in patients with advanced chronic kidney disease (CKD) [1-3]. Thiazides and related diuretic compounds represent a cornerstone of hypertension treatment for many years, while potassium-sparing diuretics are most commonly used to correct potassium deficiency in patients with hypertension or to treat primary aldosteronism [2,4]. Other diuretic classes are mostly used for more specific conditions, that is, carbonic anhydrase inhibitors for glaucoma or osmotic diuretics for cerebral oedema [1-3]. The available diuretic compounds could be also used in certain combinations to help towards effective volume control in difficult-to-treat patients with multiple underlying problems. Further, ongoing research continuously brings to light promising evidence on beneficial effects of certain diuretics on clinical conditions distinct from the traditional indications of these drugs, providing the possibility of important new therapeutic options for many patients.

This article represents the first part of a work on the clinical use of diuretics that reviews the mechanisms of action and pharmacological effects of the various classes of diuretics in order to provide insights into the proper use of these agents for different clinical situations, representing their established or emerging therapeutic indications.

2. Principles of diuretic action and classification of diuretic compounds

All diuretics in clinical use act by inhibiting Na^+ reabsorption in the renal tubules and, thus, increasing fractional excretion of Na^+ (FE_{Na}). In general, under physiological conditions of Na^+ intake, FE_{Na} remains under 1%, that is, $> 99\%$ of the filtered amount of Na^+ is reabsorbed [2,5]. Reabsorption of NaCl in renal tubules is driven by the Na^+-K^+-ATPase pump of the basolateral membrane of tubular epithelial cells, which uses energy to move Na^+ from the cell into the interstitium and blood and K^+ from the interstitium to the cell. This continuous action is responsible for retaining low Na^+ and high K^+ concentrations intracellularly, as well as keeping the cell interior electrically negative in relation to the extracellular fluid. The latter electrochemical gradient is the force driving positively charged Na^+ ions across the apical membrane into the cell. This movement takes place through specific transport pathways of the luminal membrane that differ between the various segments of the nephron, unlike the fact that the basolateral membrane Na^+-K^+-ATPase system is present in practically all tubular epithelial cells [2,5]. With the exception of osmotic agents, all other diuretics act by interfering with a specific transport system of the apical membrane. This Na^+ movement down its electrochemical gradient from the lumen to tubular cells and to interstitium is coupled by movement of water and other solutes either against or in parallel to their electrochemical gradient.

The most common and clinically useful classification of diuretic agents is related to their mechanism and, consequently, their major site of action along the nephron. Based on this, diuretic compounds can be divided into carbonic anhydrase inhibitors, osmotic agents, loop diuretics, thiazides and related sulfonamide compounds and potassium sparing diuretics, including amiloride, triamterene and aldosterone antagonists (**Table 1**) [2,4]. As the amount of Na^+ reabsorbed is different between the various segments of the nephron, the site of action greatly determines the relative efficacy of diuretic compounds, expressed by the maximal percentage of filtered

Table 1. Classification, major site of action, mechanism of action and clinical use of diuretic agents.

Diuretic agents	Major site of action	Mechanism of action	Clinical use
Carbonic anhydrase inhibitors			
Acetazolamide	Proximal convoluted tubule	Inhibition of carbonic anhydrase	Glaucoma, metabolic alkalosis, altitude sickness, diuretic resistance
Osmotic agents			
Mannitol	Proximal convoluted tubule and thick ascending limp of the loop of Henle	Osmotic effects	Cerebral oedema
Loop diuretics			
Furosemide Torsemide Bumetanide Ethacrynic acid	Thick ascending limp of the loop of Henle	Inhibition of Na^+-K^+-$2Cl^-$ co-transporter	Oedematous disorders (congestive heart failure, hepatic cirrhosis, nephrotic syndrome), renal insufficiency, hypertension in kidney disease, hypercalcaemia, hyponatraemia, SIADH, renal tubular acidosis
Thiazides and related agents			
Thiazides			
Hydrochlorothiazide Chlorothiazide Bendroflumethiazide Trichlormethiazide	Distal convoluted tubule	Inhibition of Na^+-Cl^- co-transporter	Hypertension, hypercalciuria, diabetes insipidus, mild oedema
Thiazide-related agents			
Chlorthalidone Indapamide Metolazone Quinethazone	Distal convoluted tubule	Inhibition of Na^+-Cl^- co-transporter	Hypertension, hypercalciuria, diabetes insipidus, mild oedema
Potassium-sparing agents			
Pteridine derivatives			
Amiloride Triamterene	Cortical collecting duct	Inhibition of epithelial Na^+ channel	Hypertension with potassium and/or magnesium loss, Liddle's syndrome
Aldosterone antagonists			
Spironolactone Eplerenone	Cortical collecting duct	Aldosterone-receptor blocking	Primary aldosteronism, hypertension with potassium and/or magnesium loss, secondary aldosteronism (congestive heart failure, hepatic cirrhosis, nephrotic syndrome), heart failure, resistant hypertension

SIADH: Syndrome of inappropriate antidiuretic hormone hypersecretion.

NaCl load that is excreted. In addition, the different sites of action allow for additive effects when different classes of diuretics are combined, which can be useful in specific patients with diuretic resistance [1].

3. Carbonic anhydrase inhibitors

Acetazolamide is a derivative of the sulfonamide antibiotic sulfanilamide, which was noted to cause diuresis with metabolic acidosis as a side effect due to inhibition of carbonic anhydrase. Among several chemical modifications of sulfanilamide molecule studied, acetazolamide was the one with the most desirable diuretic features [1]. As most diuretics (with the exception of spironolactone and eplerenone), acetazolamide must reach the lumen of the renal tubule to cause its effects; acetazolamide is actively secreted at the proximal tubule via the organic acid secretory pathway. In the proximal tubule, an important amount of Na^+ crosses the luminal membrane in exchange H^+, through a specific form of the Na^+-H^+-exchanger (NHE), the NHE3 (gene symbol *SLC9A3*). Na^+ crosses the basolateral membrane via the Na^+-K^+-ATPase pump and a $NaHCO_3$ transport pathway. The excreted H^+ titrate bicarbonate (HCO_3^-), which has been filtered by the glomeruli to form H_2CO_3, splits to H_2O and CO_2 with the catalysing action of carbonic anhydrase in the brush border of the proximal tubule epithelial cells. In addition, carbonic anhydrase located inside the epithelial cells catalyses the generation of H^+ and HCO_3^- from H_2CO_3; H^+ moves to the lumen through NHE3 and HCO_3^- exits across the basolateral membrane to the interstitium. The final functional

result of these events is the transport of Na^+ and HCO_3^- from the lumen to the interstitium [2,3]. Carbonic anhydrase inhibitors interfere with the enzyme activity both within the brush border and inside the cell, resulting in impaired Na^+, HCO_3^- and water reabsorption. The loss of HCO_3^- leads to metabolic acidosis, which characterises this group of agents. Increased delivery of Na^+ to the distal nephron and collecting duct results in increased exchange for K^+, which is facilitated by the negative charge created by the luminal HCO_3^-. Thus, the net effect of acetazolamide is increased Na^+, HCO_3^-, K^+ and water loss [1,2].

Because the proximal tubule absorbs the majority of filtered sodium (60 – 70%), one might expect a proximally acting diuretic to have a large effect. This is not the case, however, because compensatory processes develop. When proximal Na^+ reabsorption is inhibited, most of the Na^+ and solutes remaining in the lumen can be reabsorbed in more distal parts (mainly at the thick ascending limb of the loop of Henle). Moreover, inhibition of proximal Na^+ reabsorption increases Na^+ and solute delivery to the macula densa and activates the tubuloglomerular feedback mechanism, which suppresses glomerular filtration rate (GFR) and the amount of solutes filtered. Further, alkaline diuresis causes serum HCO_3^- to decline and less HCO_3^- to be filtered; as a result, the carbonic anhydrase-dependent component of Na^+ reabsorption in the proximal tubule becomes a less important pathway of total Na^+ reabsorption and the effect of carbonic anhydrase inhibitors declines [1,2].

Because of this weak effect and the inevitable metabolic acidosis occurring with chronic use, the use of acetazolamide as a diuretic is limited. A rare indication could be in patients refractory to loop diuretics, particularly those with heart failure, where proximal tubular reabsorption of Na^+ may increase and, thus, less Na^+ is delivered in loop of Henle [6]. Addition of acetazolamide in this setting can cause a clinically significant increase in diuresis [7,8]. However, because carbonic anhydrase takes part in intraocular fluid (aqueous humor) formation, acetazolamide and its derivative, methazolamide (developed to act on ocular carbonic anhydrase with little systemic effect), are commonly used to treat glaucoma [3,9]. Further, the systemic metabolic acidosis caused by acetazolamide can be used to correct metabolic alkalosis. This treatment is useful when metabolic alkalosis-evoked hypoventilation to correct systemic PH compromises respiratory drive and causes important hypoxemia in predisposed patients (i.e., those with chronic obstructive pulmonary disease), and especially in patients where normal saline cannot be used due to volume expansion [2,3,10]. Finally, acetazolamide was shown to be an effective treatment and prophylaxis against acute altitude sickness. This could be related to the drug-induced metabolic acidosis, but the exact mechanisms are not known [1-3]. With a half-life of about 13 h, twice-a-day dosing of acetazolamide is sufficient (**Table 2**) and steady-state concentrations are attained after 2 days of therapy [1,3]. However, as all acetazolamide is excreted in the urine, its renal elimination is compromised in patients with renal insufficiency, where specific attention should be paid [9,11,12].

4. Osmotic diuretics

Osmotic diuretics do not interfere with tubular electrolyte transport systems but act as osmotic particles in the tubular fluid [2]. Mannitol is a sugar that remains within the vascular space, is freely filtered through the glomerulus and very poorly reabsorbed [13]. Thus, after being filtered, mannitol exerts an osmotic effect throughout the length of the renal tubule, regardless of the state of hydration. This increased osmolality of the tubular fluid impairs normal tubular water reabsorption, which is driven by the osmotic gradients generated by ion transport systems in the various parts of the nephron. Osmotic diuretics wash out the medullary solute gradient and this greatly impairs the kidney urinary concentrating capacity [3,8,13]. This effect is similar to osmotic diuresis and polyuria due to high blood glucose in patients with uncontrolled diabetes mellitus. The inhibition of water reabsorption dilutes tubular fluid, which in turn predisposes to NaCl backflux, impairing in this way the ability of the proximal tubule and thick ascending limb to reabsorb Na^+ and Cl^- (**Table 1**). The increased delivery of Na^+ to distal tubular sites allows increased exchange for K^+, so that potassium is also lost. Further, the osmotic effect of mannitol in the proximal tubule inhibits HCO_3^- reabsorption, but the effect in the loop of Henle promoting Na^+ and Cl^- wasting predominates [1-3].

Mannitol is highly effective in reducing cerebral oedema (first by osmotic fluid removal from the brain and then by osmotic diuresis) and is frequently used today in patients with CNS infections, and after intracranial surgery or trauma [1-3]. Mannitol has been investigated as a preventive measure against development of acute renal failure (ARF) in high-risk patients, that is, after cardiopulmonary surgery, radiocontrast exposure and rhabdomyolysis. However, there is limited, if any, evidence showing that this strategy is more effective than simply administering sufficient parenteral fluids to ensure a brisk diuresis. Mannitol has been also used in patients with oliguric ARF in an attempt to promote diuresis; similarly, in the absence of conclusive data, assuring adequate volume status in the patient seems a better alternative [13,14]. Mannitol is eliminated quickly, with a half-life of about 1 h in patients with normal renal function [15] and for this reason it is administered in frequent time intervals (usually every 3 – 4 h) or as a continuous intravenous infusion (**Table 2**). Of note, mannitol elimination is markedly impaired in patients with advanced renal insufficiency (half-life of 36 h). Retention of mannitol in such patients can be dangerous, as it remains in the vascular space, where its osmotic effect expands blood volume with risks of precipitating heart failure [16]. For this same reason, mannitol should be avoided in patients with congestive heart failure.

5. Loop diuretics

Furosemide and ethacrynic acid were developed independently and practically simultaneously in the 1960s,

Table 2. Pharmacologic and pharmacokinetic characteristics of diuretic agents.

Diuretic agents	Chemical class	Maximum effect (% of filtered load of sodium)	Half-life (hours)	Duration of action (hours)	Daily dosage (dosing schedule)
Carbonic anhydrase inhibitors					
Acetazolamide	Sulfonamide derivative	3 – 5	13 (prolonged in ESRD)	16	250 – 1000 mg (b.i.d.)
Osmotic agents					
Mannitol	Sugar	20 – 25	1 (up to 36 h in ESRD)	2	50 – 200 g (continuous i.v. infusion or i.v. infusion every 3 – 4 h of 20% solution)
Loop diuretics	Sulfonamide derivatives	20 – 25			
Furosemide			1.5 – 2 (prolonged in ESRD)	4 – 6	20 – 480 mg (b.i.d. or t.i.d.)
Torsemide			3 – 4 (unchanged in ESRD)	12	5 – 40 mg (q.d. or b.i.d.)
Bumetanide			0.3 – 1.5 (unchanged in ESRD)	4 – 6	0.5 – 5 mg (b.i.d. or t.i.d.)
Ethacrynic acid			-	12	25 – 100 (q.d.)
Thiazides and related agents	Sulfonamide derivatives	5 – 8			
Thiazides					
Hydrochlorothiazide			3 – 10	12 – 18	12.5 – 50 mg (q.d.)
Chlorothiazide			15 – 25	6 – 12	125 – 500 mg (q.d. or b.i.d.)
Bendroflumethiazide			2.5 – 5	18	2.5 – 5 mg (q.d.)
Trichlormethiazide			1 – 4	24	1 – 4 mg (q.d.)
Thiazide-related agents					
Chlorthalidone			24 – 55	24 – 72	12.5 – 50 mg (q.d. or every other day)
Indapamide			6 – 15	24 – 36	1.25 – 2.5 mg (q.d.)
Metolazone			-	24	0.25 – 2.5 mg (q.d.)
Quinethazone			10	18 – 24	25 – 100 mg (q.d.)
Potassium-sparing agents					
Pteridine derivatives	Pteridine derivatives	2 – 3			
Amiloride			17 (prolonged in ESRD)	24	5 – 10 mg (q.d.)
Triamterene			3 (active metabolite = 3) (prolonged in ESRD)	12	50 – 150 mg (q.d.)
Aldosterone antagonists	Mineralocorti-coid analogues	2 – 3			
Spironolactone			1.5 (active metabolites = 15)	8 – 12	25 – 100 mg (q.d.)
Eplerenone			3 – 4	12	25 – 100 mg (q.d.)

Modified from [1,4,67].
b.i.d.: Twice daily; ESRD: End stage renal disease; i.v.: Intravenous; q.d.: once daily; t.i.d.: Three times a day.

followed by other active sulfamoylanthranilic acids, such as bumetanide and torsemide [1]. Loop diuretics represented a major breakthrough, due to their potent effect that made them useful in patients who did not respond adequately to other diuretics. Due to extensive binding to serum albumin (> 95%), very little amount of these agents reaches the tubular lumen by filtration and they are almost exclusively transported into the proximal tubule lumen by active secretion via the organic acid secretory pathway [17]. Loop diuretics act at the thick ascending limb of the loop of Henle, where ~ 20 – 30% of filtered NaCl is reabsorbed [18]. Because a maximally effective dose of a loop diuretic can cause excretion of 20 – 25% of filtered Na^+ (**Table 1**), these agents can practically block all Na^+ reabsorption by this nephron segment [1].

The most important ion transport pathway of the apical membrane of epithelial cells of the thick ascending limb is the electroneutral Na^+-K^+-$2Cl^-$ co-transporter (NKCC2, gene symbol *SLC12A1*) [3,19,20], which passively carries 1 Na^+, 1 K^+ and 2 Cl^- ions into the cell based on the electrochemical Na^+ gradient generated by the Na^+-K^+-ATPase pump of the basolateral membrane. An important amount of K^+ transported via the Na^+-K^+-$2Cl^-$ co-transporter returns in the lumen via K^+-channels of the luminal membrane. Thus, the net effects of this pathway are NaCl reabsorption and a voltage across the tubular wall oriented with the lumen positive in relation to the interstitium [2,21]. Loop diuretics bind to the Na^+-K^+-$2Cl^-$ transport protein [19,22] and inhibit its action, impairing in this way reabsorption of Na^+, K^+ and Cl^- at the thick ascending limb of the loop of Henle. Apart from this inhibition of K^+ reabsorption, they also promote K^+ secretion from distal tubular sites due to increased delivery of Na^+. In addition to the above, the lumen positive voltage at the thick ascending limb is important for Ca^{2+} and Mg^{2+} reabsorption at this part of the nephron; thus, loop diuretics also cause loss of Ca^{2+} and Mg^{2+} with the urine [1-3,21,23]. As the thick ascending limb is impermeable to water, solute removal from this part of the nephron is responsible for the counter-current multiplication and the generation of the hypertonic medullary interstitium that later serves as the osmotic driving force for water absorption at the collecting duct under the effect of arginine vasopressin (AVP). Inhibition of Na^+-K^+-$2Cl^-$ from the loop diuretics prohibits solute removal at the thick ascending limp and decreases this osmotic driving force and, thereby, impairs the ability of the kidney to generate concentrated urine [1-3]. Further, in the physiologic kidney, solute removal at the thick ascending limb serves to dilute the tubular fluid and promotes free water generation when necessary; thus, loop diuretics can also blunt the ability of the kidney to produced maximally diluted urine [2,3].

Administration of loop diuretics has been also associated with hemodynamic changes in the systemic circulation and renal microcirculation. Intravenous loop diuretics have a short-lasting vasodilating effect by an endothelium-dependent hyperpolarising action [3,24]. The occurring venodilatation can produce decrease in cardiac preload, explaining the immediate symptomatic improvement often occurring in patients with acute pulmonary oedema before any diuretic effect [1]. However, loop diuretic can also cause activation of the sympathetic nervous system (SNS) and the renin–angiotensin system (RAS), causing vasoconstriction and increased afterload [25]. With regard to renal hemodynamics, loop diuretics tend to maintain or increase GFR even in the case of volume depletion due to prostaglandin-mediated dilation of the afferent arteriole and blocking of the tubuloglomerular feedback mechanism [2].

When loop diuretics are used, a number of important issues related to their pharmacokinetics should be remembered in order to ensure their clinical efficacy. Furosemide and bumetanide have rapid action but short half-lifes. After intravenous administration, response begins within minutes and after oral dosing peak response occurs within 30 – 90 min; in both cases, response continues for 2 – 3 h and, therefore, in many patients, these drugs must be administered multiple times a day [1,21]. Torsemide has a somewhat longer half-life and duration of action and can therefore be administered less frequently (**Table 2**) [26]. In any case, the traditional dosing intervals of all loop diuretics exceed the duration of time when effective amounts of drug are at the site of action. In the time during which there are inadequate amounts of diuretic at the site of action, the nephron avidly reabsorbs Na^+, causing the so-called 'postdiuretic' or 'rebound' Na^+ retention. This Na^+ retention can possibly nullify the previous natriuresis, especially if a short-acting loop diuretic is administered once-daily and NaCl intake is high [2,21,27,28]. This problem is amplified if dietary NaCl intake and ingestion do not correspond to the drug action [27]. Another issue of importance is bioavailability; bumetanide and torsemide are completely absorbed in gastrointestinal track (≥ 80%), whereas, on average, 50% of a dose of furosemide is absorbed; thus, the oral dose of furosemide needs to be about twice the intravenous [1,3,21]. Unfortunately, oral furosemide has enormous variability of absorption both among patients and within an individual patient from day to day (ranging from 10 to 100%) [29], whereas concomitant ingestion of furosemide and bumetanide with food dramatically decreases their bioavailability [30]. Torsemide does not have these disadvantages [31] and this can be clinically important, as shown from a recent study reporting fewer hospitalisations and better quality of life in patients with heart failure treated with torsemide compared with furosemide [32].

With regard to metabolism, 50% of furosemide is excreted unchanged into the urine and the remainder is conjugated to glucuronic acid in the kidney [33]. Bumetanide and torsemide have substantial metabolism (50 and 80%, respectively), but most of this is hepatic rather than renal [26,34]. Thus, in patients with renal insufficiency, the plasma half-life and the duration of action of furosemide is prolonged due to decrease of both urinary excretion and renal conjugation, whereas the half-lifes of bumetanide and torsemide remain unchanged, because the liver provides an alternative route for

Table 3. Conditions of diminished response to loop diuretics and respective maximum effective doses.

Clinical condition	Renal insufficiency		Nephrotic syndrome*	Cirrhosis*	Heart failure*
	Moderate (CrCl 20 – 50 ml/min)	Severe (CrCl < 20 ml/min)			
Mechanism of diminished response to diuretic	Impaired delivery to the site of action		Diminished nephron response. Binding of diuretic to urinary protein	Diminished nephron response	Diminished nephron response
Therapeutic strategy to achieve response	Increased frequency of effective dose. Sufficient dose to attain effective excretion rates at the site of action		Increased frequency of effective dose. Sufficient dose to attain effective excretion rates of unbound diuretic at the site of action	Increased frequency of effective dose	Increased frequency of effective dose
Maximum effective doses (mg)					
Furosemide i.v.	80 – 160	200	120	40	40 – 80
Furosemide p.o.	160	400	240	80	80 – 160
Bumetanide i.v. or p.o.	6	10	3	1	1 – 2
Ethacrinic acid i.v. or p.o.	100	250	150	50	50 – 100
Torsemide i.v. or p.o.	50	100	50	20	20 – 40

Modified from [1,3,21].

* With preserved renal function.

CrCl: Creatinine clearance; i.v.: Intravenous, p.o.: Per os.

elimination (**Table 2**) [3,8,21]. In any case, however, renal disease impairs delivery into the tubular lumen of all loop diuretics, as their secretion in the lumen through the organic acid pathway is competed by endogenous organic acids that accumulate as kidney function decreases. Thus, larger doses of these drugs should be administered to attain effective drug amounts at the site of action [3,8,21,35]. In patients with hepatic disease, the plasma half-lifes of bumetanide and torsemide are prolonged, an effect that can paradoxically enhance response [21,36].

Loop diuretics are the most effective diuretics available, and, therefore, mostly helpful agents in patients with oedematous disorders such as congestive heart failure, severe hepatic cirrhosis and the nephrotic syndrome, especially if creatinine clearance is less than about 40 ml/min/1.73 m^2, when thiazide diuretics as single agents are unlikely to be clinically effective, as discussed later [1,21]. These agents are also the diuretics of choice for hypertension or volume control in patients with CKD and creatinine clearance lower than the aforementioned levels. In patients with CKD, the pharmacodynamics of loop diuretics are not significantly altered, as residual nephrons seem to respond 'normally,' (i.e., with a FE_{Na} is similar to that of healthy subjects [37]), but the overall (absolute) Na^+ excretion is lower due to the decrease in the filtered load of Na^+ [1,3,21,35]. Further, due to the aforementioned impaired delivery of diuretic into the urine, attaining maximal response requires higher doses; the maximal doses have been determined in clinical studies (**Table 3**). Of note, larger doses than those depicted in **Table 3** will not increase response, as the plateau of the dose–response curve has been reached, but will enhance the risk of toxicity; thus, the only way to increase cumulative response is to administer effective doses on multiple occasions per day [1,8,21]. Importantly, although most such patients will require large doses, their treatment should start from small doses, followed by upward titration according to clinical response towards the goal of treatment; this is particularly required for oral furosemide, due to the aforementioned problematic pharmacokinetics.

In patients with heart failure, cirrhosis or nephrotic syndrome, the pharmacodynamics of loop diuretics are altered so that maximal response is also lower. One possible mechanistic explanation for this could be the increased proximal and/or distal Na^+ reabsorption. Studies in rats with congestive heart failure have shown upregulation of the transcription of Na^+-K^+-Cl^- co-transporter in the thick ascending limb of Henle [38]; thus, increased expression of Na^+-K^+-Cl^- co-transporter in heart failure may represent another explanation for a change in the pharmacodynamics of loop diuretics [38]. Whatever the cause, the clinical translation of this phenomenon is that the diminished response is not improved by administering large doses, and, thus, ceiling doses of loop diuretics in patients with heart failure and cirrhosis without renal insufficiency are modest [1,21]. In patients with nephrotic syndrome, additional

pharmacokinetic problems have been hypothesised, which decrease the amount of loop diuretic in the site of action, inadequate secretion from blood to lumen of the nephron due to hypoalbuminaemia and consequent higher volume of drug distribution or alternatively binding of the loop diuretic to albumin in the tubular lumen [1,21,35]. Both these hypotheses are supported by animal studies [39,40], leading to clinical strategies of infusing a loop diuretic together with albumin in order to increase the amount of the diuretic in the site of action. However, recent studies in nephrotic patients with serum albumin > 2 g/dl that co-administered albumin with furosemide [41,42], or studies using an agent to displace furosemide from urine albumin [43], showed no or minimal improve in response. Thus, effective diuresis in such patients requires ceiling doses of loop diuretics with frequent dosing, strict NaCl restriction and combination with other diuretics [21].

Use of loop diuretics in the treatment of uncomplicated hypertension is less advisable, mainly due to their very short duration of action in relation to thiazides. Previous clinical studies have shown that even twice-daily furosemide is less effective than hydrochlorothiazide [44,45], while producing similar hyperuricaemia and hypokalaemia. Torsemide with the longer duration of action might be more useful as an antihypertensive agent [46]. As loop diuretics cause calciuresis they can therefore be used to treat hypercalcaemia, but only after volume depletion associated with hypercalcaemia is corrected, as the latter may be enough to correct the disorder [47,48]. Loop diuretics can be also helpful in treating hyponatraemia, as they cause excretion of water in excess of sodium. For this to happen, diuretic-induced volume losses should be replaced with iso- or hypertonic saline depending on the desired speed of correcting the hyponatraemia [49]. Finally, in some patients with distal renal tubular acidosis who are unable to maintain an adequate systemic pH with conventional therapy, loop diuretics could help towards correction of the metabolic acidosis by allowing excretion of acid urine [1] through increased H^+ secretion in the distal nephron [50].

Moreover, research in the field of diuretics has brought to light promising evidence that diuretic agents already in clinical use for several years may exert additional beneficial effects beyond diuresis. It has been reported that the administration of torsemide in animal models of heart failure was associated with improved left ventricular function and amelioration of progression of cardiac fibrosis [51]. Torsemide-treated patients have been shown to have decreased serum concentrations of the C-terminal propeptide of procollagen type I, a biochemical marker of myocardial fibrosis, in comparison with furosemide-treated patients. The potential beneficial effect of torsemide prolonged-release formulation in prevention of cardiac fibrosis in patients with advanced heart failure is investigated in the ongoing TORAFIC trial, in which 142 patients with New York Heart Association (NYHA) III – IV heart failure are randomised to receive treatment with torsemise (10 – 40 mg daily) or furosemide (40 – 160 mg daily) for 8 months. The primary end point is difference between treatment groups in the change of C-terminal propeptide of procollagen type I [52]. Future studies with these agents evaluating hard cardiovascular outcomes in patients with heart failure are also required to fully elucidate this issue.

6. Thiazides and thiazide-related diuretics

Thiazides were developed by chemical modifications of the sulfa nucleus of acetazolamide in an attempt to produce a diuretic that would provide NaCl diuresis instead of $NaHCO_3$ diuresis [53]. Chlorothiazide was the first thiazide compound discovered followed by additional agents with the same pharmacology but different pharmacokinetic features. Other modifications of the sulfa nucleus resulted in quinethazone, metolazone, chlorthalidone and indapamide, which have pharmacological effects similar to those of the classical thiazides but represent a different chemical category [1]. As in the case of loop diuretics, the above agents circulate in the blood stream bound with albumin and are actively secreted in the proximal tubule lumen via the organic anion pathway [1,2]. Thiazides and related sulfonamide compounds act mainly at the distal convoluted tubule (**Table 1**), where ~ 5 – 10% of filtered NaCl is reabsorbed [18]. At this nephron segment, Na^+ and Cl^- enter the cell through the luminal membrane via an electroneutral NaCl co-transport pathway (NCC, gene symbol *SLC12A3*) [2,19,54]. This pathway is blocked by thiazides and related agents, resulting in impaired Na^+ and Cl^- reabsorption. Of note, the same pathway is genetically inactive in Gitelman's syndrome and the phenotype of this syndrome is very similar to the effects of thiazides [55,56]. Due to increased delivery of Na^+ in the collecting duct, the exchange of Na^+ with K^+ is also increased, resulting in K^+ wasting. As the distal tubule is relatively impermeable to water and the normal NaCl reabsorption contributes to tubular fluid dilution, thiazides impair the kidney diluting capacity but have no effect on the kidney concentrating capacity [1-3]. Further, these agents impair Mg^{2+} reabsorption, but, in contrast to loop diuretics, stimulate Ca^{2+} reabsorption. This can be a consequence of either increased proximal Na^+ and Ca^{2+} reabsorption due to thiazide-related decrease in extracellular volume or increased distal Ca^{2+} reabsorption. The latter action could be mediated through increased $3Na^+$-Ca^{2+} exchange at the basolateral membrane following thiazide-induced reductions in intracellular Na^+ or through opening of voltage-dependent transient cation channels due to electrically negative tubular cell interior resulting from Cl^- re-entry from the interstitium [2,57].

The most common use of thiazide and thiazide-related diuretics is essential hypertension. Numerous clinical trials have shown the clinical efficacy of these compounds, as well as the reductions in cardiovascular morbidity and mortality resulting from their BP lowering effect; thus, thiazides are currently recommended as first-line choices for the treatment of essential hypertension, as monotherapy or in combination with other agents [58,59]. Initial doses of a thiazide produce decreases in extracellular volume and consequently lowering

of BP. Systematic (RAS, SNS) and intrarenal homeostatic mechanisms cause increased proximal tubule Na^+ reabsorption and re-establish the steady-state between sodium intake and excretion within 3 – 9 days, whereas with chronic use extracellular volume returns partially toward normal [60]. However, the antihypertensive effect is maintained due to chronic decrease in peripheral vascular resistance [61,62]. Thiazide-related Ca^{2+} reabsorption is useful for patients with nephrolithiasis and idiopathic hypercalciuria, as it decreases Ca^{2+} excretion by 40 – 50% and, consequently renal stone formation [63], at the cost of a slight elevation in serum Ca^{2+} levels [4]. Further, the impairment of renal maximal diluting capacity by thiazides is helpful in patients with nephrogenic diabetes insipidus, in which thiazides may reduce urinary output by up to 50%. Although the natriuretic efficacy of thiazides is limited compared to loop diuretics, they can be sufficient in mild edematous disorders, unless the patient has also reduced GFR [1,2]. Thiazides can be also helpful in patients treated with a loop diuretic that develop severe resistance. In these patients, NaCl delivery at the distal convoluted tubule, the segment sensitive to thiazides, is increased; further, chronic treatment with a loop diuretic through increased solute delivery to the distal tubule induces hypertrophy of the epithelial cells, and increases the expression of transport proteins and the Na^+ transport capacity of that segment. Thus, in such cases, the natriuretic efficacy of thiazides is increased and their addition to the regimen can provide important increases in diuresis [2,64,65].

An important advantage of the most widely used thiazides and related diuretics (hydrochlorothiazide, chlorthalidone and indapamide) is the long duration of action. Of note, the duration of the antihypertensive effect is greater that the duration of the diuretic effect [66], which is depicted in **Table 2**, making once-daily dosage possible. Thiazides have a very shallow dose–response curve, meaning that there is little difference between the lowest and the maximally effective dose listed in **Table 2** [1,67]. Clinical evidence suggests almost similar antihypertensive efficacy between low and high doses (i.e., hydrochlorothiazide 12.5 mg versus 25 or 50 mg), with lower complications rates with small doses [4,68]. Thus, hypertension therapeutics in recent years has been shifted towards lower doses of these agents. When thiazides are used in combination therapy, even lower doses (i.e., hydrochlorothiazide 6.25 mg) may be quite effective due to synergistic effect with other antihypertensive classes [58,59]. The most important problem regarding the clinical use of these agents is that their natriuretic effect is lost when GFR is reduced below about 40 ml/min/1.73 m^2 [1,67,69] with the exception of metolazone, which is still active until about 20 ml/min [70]. This is because in CKD active secretion of thiazides in the lumen through the organic acid pathway is progressively reduced, due to accumulation of endogenous organic acids that compete with thiazides for transport [4,71]. If given in high enough doses, thiazides would probably work in CKD patients, but this strategy is not advisable given the low efficacy of thiazides compared to loop diuretics and the risk of metabolic side effects with high doses [71]. The only possible indication of thiazides and related agents in CKD is in combination with loop diuretics in the patient that is severely resistant, as mentioned above.

7. Potassium-retaining diuretics

Potassium-retaining diuretics can be divided in two sub-categories: those inhibiting the epithelial Na^+ channel of the collecting duct (amiloride and triamterene), which are pteridine analogues and those blocking aldosterone receptors (spironolactone and eplerenone). Both act primarily at the cortical part of the collecting duct (and to a lesser extend at the final segment of the distal convoluted tubule and the connecting tubule), where only about 3% of the filtered Na^+ load is reabsorbed [1-3]. To produce their actions, amiloride and triamterene are actively secreted into the lumen at the proximal tubule via the pathway for organic bases; spironolactone and eplerenone are the only diuretics that do not enter the tubular lumen, as they act in the cytoplasm of the principal cells of the collecting duct. In this part of the nephron, Na^+ moves into the principal cells through the apical membrane via an epithelial Na^+ channel (ENaC), following its electrochemical gradient generated by the Na^+-K^+-ATPase pump of the basolateral membrane [1,2,72-74]. Na^+ movement through the apical membrane is electrogenic, creating a voltage across the tubule wall with the lumen negative in relation to the interstitium and blood. This electric gradient is responsible to drive K^+ movement from the epithelial cell to the lumen through a ion channels that are not fully characterised [1,2]. In addition, this voltage promotes electrogenic H^+ secretion into the tubular lumen; thus, factors that stimulate Na^+ reabsorption indirectly promote urine acidification. Through this process, the principal cells take an indirect part in the distal acid–base transport, which is regulated by the neighbour intercalated cells through complex mechanisms [50,75]. Amiloride and triamterene selectively block the Na^+ entry through ENaC. Aldosterone and eplerenone competitively block the aldosterone mineralocorticoid receptors in the cytoplasm of principal cells, thus, inhibiting aldosterone action [1,2]. Physiologically, after aldosterone binding to the receptor, the hormone–receptor complex translocates to the nucleus of the cell, where they stimulate gene expression and protein synthesis of elements of the cellular Na^+ transport machinery (i.e., subunits of the Na^+-K^+-ATPase pump and ENaC) [76]. The final effects of both these drug categories are impairment of Na^+ reabsorption, coupled with increased K^+ and H^+ secretion at the collecting duct.

As only a small amount of Na^+ is reabsorbed at the collecting duct, potassium-sparing diuretics are not very potent agents in most patients. Thus, amiloride and triamterene are mostly used in the treatment of hypertension in combination with other agents to correct potassium deficiency in patients without mineralocorticoid excess. These agents have been also used to correct magnesium deficiency in

hypertension, although the exact mechanism of this action is unknown [1,4]. Single-pill combinations of amiloride or triamterene with thiazide diuretics were widely prescribed antihypertensive drugs in the US and other countries. It must be noted, however, that using these combinations is not recommended as a first-step in hypertension treatment, because only about 5% of patients receiving thiazide diuretics become potassium-depleted and need a potassium-sparing agent. Prescribing such combinations as prophylaxis against hypokalaemia exposes the majority of patients at a risk of hyperkalaemia, which is more life threatening than potassium depletion [1,77]. Amiloride and triamterene are the drugs of choice for patients with full-blown Liddle's syndrome, which is caused by gain-of-function mutations of the gene expressing the ENaC; the consequent overactivity of ENaC leads to a state of 'pseudoaldosteronism' characterised by volume expansion and hypertension. These patients respond well to the treatment with amiloride and triamterene which selectively inhibit the action of ENaC; in contrast, aldosterone-blockers are not helpful in Liddle's syndrome, because RAS is downregulated [4,78]. To exert its action, triamterene must be converted to an active metabolite, which is a sulfate ester, by the liver, a process that can be impaired in patients with liver disease, making the drug ineffective; thus, in patients with liver disease amiloride should be preferred. Further, amiloride has a longer half-life in relation to triamterene (**Table 2**) [1].

Spironolactone has been used in the treatment of essential hypertension for many years [79] and eplerenone has been shown to have antihypertensive efficacy similar to common antihypertensive agents [80]. However, these drugs are mostly used in essential hypertension in combination with other diuretics to avoid potassium deficiency [4]. In contrast, blocking the aldosterone-receptor makes spironolactone and eplerenone the drugs of choice in patients with mineralocorticoid excess. Spironolactone is the main therapy in patients with primary aldosteronism due to bilateral adrenal hyperplasia and in patients with aldosterone-producing adrenal adenomas (Cohn's syndrome) until the surgical resection of the tumour, those unwilling or unable to undertake surgery and those that remain hypertensive after surgery [81]. Eplerenone is a more specific blocker of the mineralocorticoid receptor, without the estrogenic side effects that occur with high-doses of spironolactone due to stimulation of estrogen-receptors [82]. Spironalactone has been shown to be effective also in patients with secondary hyperaldosteronism. The most common clinical setting is the patient with hepatic cirrhosis and ascites, where spironolactone can be used in combination with loop diuretics, or as a single agent, because recent data suggest spironolactone to be more effective than a loop diuretic in such patients [2]. Although spironolactone has a short half-life, it seems that activity resides in several metabolites with half-lifes of about 15 h; thus, its total duration of action is > 1 day and can be dosed once-daily (**Table 2**) [1,2].

In view of the accumulating evidence supporting a major role of aldosterone in target-organ damage and the fact that aldosterone levels escape suppression during long-term treatment with ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) [83,84], several recent studies have investigated the role of aldosterone blockers in protecting the heart, brain, kidney and blood vessels. Two recent clinical trials have shown that adding spironolactone in patients with chronic heart failure [85] or eplerenone in patients with heart failure after myocardial infarction [86] on top of therapy including ACEIs or ARBs and diuretics reduced morbidity and mortality. This has led to recommendations to include aldosterone-antagonists in the treatment of patients with NYHA class III – IV heart failure. However, doctors need to pay particular attention at monitoring potassium levels when prescribing these drugs, as the increase in their use have been associated to a major increase of hospital admissions due to hyperkalaemia [87]. Smaller studies have also shown that both spironolactone and eplerenone are able to reduce urine albumin excretion in patients with diabetic nephropathy already receiving an ACEI or ARB [88-90] but long-term data need to be available before this therapy is included in relevant guidelines. Finally, following reports on high prevalence of aldosteronism in resistant hypertension [91], recent studies have examined the effect of aldosterone-antagonists added to existing antihypertensive regimens in patients with resistant hypertension, showing that these agents have a major BP lowering effect independent of the presence of primary aldosteronism [92,93]. Thus, addition of these agents in patients truly following into the definition of resistant hypertension can be a great help [91,94].

8. Conclusion

Diuretics are potent drugs that have been used broadly and successfully for > 50 years in the treatment of major diseases of internal medicine, such as hypertension and common oedematous disorders (cardiac failure, nephrotic syndrome, hepatic cirrhosis). Certain diuretics have been also used for years in the treatment of more specific conditions, such as glaucoma, cerebral oedema, hypercalcaemia, hypercalciuria and diabetes insipidus. Ongoing research in the field produces possible new therapeutic indications for certain diuretic compounds (i.e., heart and renal protection for aldosterone blockers). For both established and emerging indications, however, deep knowledge of the pharmacology of each diuretic class remains the key tool towards the effective clinical use of these valuable therapeutic tools for the benefit of our patients.

9. Expert opinion

Carbonic anhydrase inhibitors and osmotic diuretics, at present, are mostly used for specific conditions. Acetazolamide and its derivative, methazolamide, are widely used for the treatment of glaucoma; however, acetazolamide can be particularly helpful in rare but difficult clinical situations, that is, in patients on loop diuretics who develop treatment resistance,

and in patients with metabolic alkalosis, reduced respiratory drive and volume expansion. Mannitol is extensively used in neurological and neurosurgical departments, as well as in intensive care units to reduce cerebral oedema. However, in our experience, the clinical use of these agents is not without consequences. We have noted several cases of acute pulmonary oedema due to mannitol retention in the vascular space and volume expansion when the dose of mannitol was not adjusted according to the underlying renal function. Moreover, we have witnessed many cases of pre-renal ARF following extensive diuresis when mannitol was used for cerebral oedema in predisposed patients (i.e., older individuals with hemorrhagic strokes) and volume losses were not carefully replaced. These clinical problems highlight the necessity of careful estimation of the patient's renal function (with use of creatinine clearance or GFR instead of serum creatinine values) before mannitol is used and maintenance of fluid balance afterwards.

Loop diuretics are successfully used for many years in patients with oedematous disorders such as congestive heart failure, hepatic cirrhosis and the nephrotic syndrome, as well as for volume and BP control in patients with CKD. However, to ensure the clinical efficacy of these agents, it is extremely important to pay particular attention to their pharmacokinetics. The most important problem is the extremely short half-lifes and durations of action of furosemide and bumetanide, which is followed by 'rebound' Na^+ retention in the time when there are inadequate amounts of diuretic at the site of action. Although this 'rebound' phenomenon is rather well described by background data, the relevant clinical studies are few [27] and, thus, the importance of correct dosing of loop diuretics has not been adequately highlighted. In our experience, the majority of clinicians prescribe furosemide once daily or at most twice a day, which can have important consequences. Another pharmacokinetic problem is the reduced delivery of loop diuretics in the site of action in patients with renal insufficiency, which requires additional dose adjustments according to the degree of renal function.

Although loop agents are widely used in several clinical settings, the clinical implications of the short half-life and the problematic bioavailability of furosemide have not been adequately studied. This is particularly important on the basis that torsemide has longer half-life and duration of action so that it can be dosed twice daily, and it is almost fully absorbed in the gastrointestinal tract, but is not commercially available in many countries. Studies involving head-to-head comparisons of torsemide with furosemide are very limited [32]. Thus, one direction for future research should be clinical studies on the natriuretic and diuretic efficacy of loop agents with short half-lifes (i.e., furosemide and bumetanide) given once versus multiple times daily; this is necessary in order to further highlight the importance of adequate dosing of these drugs and to ensure proper prescription from the medical community. Moreover, it has been reported that torsemide may exert beneficial effects beyond diuresis that is, amelioration of progression of cardiac fibrosis in patients with heart failure [51]; we anticipate the results of the ongoing TORAFIC trial, which will shed light on this important issue [52]. To further evaluate possible cardiovascular differences between loop diuretics, studies comparing the effects of these agents on hard cardiovascular outcomes in patients with heart failure are also required. Last but not least, future research could be also directed towards the development of new agents with prolonged half-lifes and/or extended release formulations of short-acting loop diuretics; given the wide use of this class, such compounds could be of extreme help for many patients.

With regard to thiazides and thiazide related diuretics, although their natriuretic efficacy is lower than that of loop diuretics, due to their ability to chronically reduce peripheral vascular resistance and to the major pharmacokinetic advantage of long duration of action, they represent the cornerstone of antihypertensive therapy for many years. Thiazides can also offer sufficient volume control in mild oedematous disorders, and additional help in patients treated with a loop diuretic that develop resistance. However, addition of a thiazide in patients with resistance to loop diuretics is largely based on empiric observations and much less in proper studies; thus, the optimum combination therapy in patients resistant to diuretic treatment is another field that needs to be properly tested in future clinical trials. The major clinical problem of thiazide use is their decreased natriuretic effect in patients with GFR < 40 ml/min/1.73 m^2 due to their reduced delivery in the lumen, similar with the loop diuretics. In contrast to loop diuretics, however, increasing the dose of a thiazide in patients with CKD is not advisable, given the overall low diuretic efficacy of thiazides and the risk of metabolic side effects with high doses. Although this strategy is reasonable, it should be noted that there are still several issues that have not been clearly answered from clinical research, including: i) the exact level of GFR where each of the thiazide compounds abolishes its efficacy and ii) the possibility that an increased dose of a thiazide would provide better 24 h BP and volume control compared to a loop diuretic (especially if the later is short-acting). Future research in this direction may generate additional choices for our therapeutic armamentarium for patients with CKD.

Due to the small natriuretic efficacy and the potassium-retaining property, amiloride and triamterene are mainly used in the treatment of hypertension in combination with other diuretics to correct potassium deficiency in patients without mineralocorticoid excess. The aldosterone receptor blockers spironolactone and eplerenone have also important antihypertensive efficacy and can also be used in essential hypertension with hypokalaemia. However, the main indication of spironolactone is patients with primary aldosteronism due to adrenal hyperplasia and those with adrenal adenomas until surgery. Eplerenone is a molecule without the estrogenic side effects that occurs with high doses of spironolactone and appears as a better choice for patients requiring chronic treatment, but is much more expensive. In recent years, background and clinical studies provided important evidence

for a beneficial role of aldosterone blockers in target-organ damage, opening new and exciting research avenues. Both spironolactone and eplerenone were shown to reduce cardiovascular morbidity and mortality when added on recommended treatment in patients with heart failure. Similarly, spironolactone and eplerenone were found to reduce albuminuria in patients with diabetic nephropathy. The possibility of an additional renoprotective effect together with the safety of such combination therapy in these patients is without doubt another important issue to be examined by future trials with hard renal outcomes. Finally, recent reports suggest both high prevalence of aldosteronism and high efficacy of aldosterone blockers in patients with resistant hypertension; as the phenomenon of resistant hypertension was until recently understudied and treatment recommendations remained largely empiric [91,94], detailed evaluation of the effects of aldosterone blockers is one important direction in this emerging research field.

Research on the field of diuretics has also brought to light promising evidence on the potential use as diuretics of several investigational drug classes. In the early 1990s, clinical studies have shown that brain natriuretic peptide (BNP) infusion in humans increases diuresis and natriuresis and promotes relaxation of vascular smooth muscle cells, resulting in vasodilation and hypotension [95]. In 2001, nesiritide, a recombinant form of human BNP, was approved by the FDA for treatment of acutely decompensated congestive heart failure on the basis of results of clinical trials showing that this agent reduces capillary wedge pressure and improves dyspnea in such patients [95,96]. Despite the favourable natriuretic effects of this drug, two recent meta-analyses have shown that nesiritide treatment might be associated with renal function deterioration and increased short-term mortality [97,98]. Thus, in recent years, neziritide has fallen out of favour in the treatment of acute decompensated heart failure, although the findings of the above meta-analyses met severe criticism. Future clinical trials are, therefore, required to shed light on the issue of safety and tolerability of neziritide in these patients.

In addition to the above, the better understanding of the pathophysiologic role of the upregulation of AVP in several clinical conditions characterised by volume overload and the recent description of the molecular structure and function of its receptors led to development of a novel class of drugs antagonising the antidiuretic and vasoconstricting actions of this hormone [99,100]. Thus, several non-peptide AVP-receptor antagonists, also termed 'vaptans', have been investigated in animal and human studies and have been shown to exert a potent aquaretic action and increase urine volume and plasma sodium levels in a dose-dependent manner without altering BP and heart rate [99,100]. Conivaptan was the first AVP-receptor antagonist approved by the FDA for the treatment of euvolaemic hyponatraemia in the form of intravenous infusion [99]. AVP-receptor antagonists were shown to be useful in other clinical states characterised by volume overload (i.e., patients with heart failure) and the findings deriving from clinical studies were initially encouraging, showing beneficial short-term effects of these agents (i.e., alleviation of symptoms, aquaresis without worsening of hyponatraemia or renal function) [101,102]. However, the recent long-term Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial showed that AVP-receptor antagonists did not improve mortality and did not reduce the incidence of hospitalisations in patients with heart failure [103]. Additional research is required to fully elucidate the role of these drugs in the modern treatment of heart failure as well as in other clinical states characterised by volume overload and AVP upregulation, for the benefit of patients.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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