

EXPERT OPINION

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Diuretics in the treatment of hypertension. Part 2: loop diuretics and potassium-sparing agents

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Introduction: Diuretics enhance the renal excretion of Na⁺ and water due to a direct action at different tubular sites of the nephron where solute re-absorption occurs.

Areas covered: This paper focuses on the mechanism of action, pharmacodynamics, antihypertensive effects, adverse effects, interactions and contraindications of loop diuretics and potassium-sparing agents (including mineralocorticoid receptor antagonists (MRAs) and epithelial Na⁺ channel blockers).

Expert opinion: Loop diuretics are less effective than thiazide diuretics in lowering blood pressure, so that their major use is in edematous patients with congestive heart failure (HF), cirrhosis with ascites and nephritic edema. MRAs represent a major advance in the treatment of resistant hypertension, primary and secondary hyperaldosteronism and in patients with systolic HF to reduce the risks of hospitalization and of premature death. Potassium-sparing diuretics when coadministered with diuretics (thiazides and loop diuretics) working at more proximal nephron locations reduce the risk of hypokalemia and hypomagnesemia and the risk of cardiac arrhythmias. At the end of the article, the basis for the combination of diuretics with other antihypertensive drugs to achieve blood pressure targets is presented.

Keywords: arterial hypertension, drug combinations, loop diuretics, mineralocorticoid receptor antagonists, potassium-sparing agents

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1. Introduction

Diuretics are drugs that increase urine output by the kidney (i.e., promote diuresis). Their primary action is to decrease the re-absorption of Na⁺ (and Cl⁻) and water from the filtrate due to a direct action at different segment sites of the renal tubular system [1-3], increased water loss being secondary to the increased excretion of NaCl. They also modify the renal handling of other cations and anions and uric acid and, sometimes, renal hemodynamics. Diuretics are the mainstay of treatment for hypertension and edematous states characterized by excess extracellular fluid, including heart failure (HF), chronic kidney disease (CKD), nephrotic syndrome and cirrhosis with ascites. Diuretics can be classified, according to their chemical structure, the major site of action within the nephron and the type of diuresis that they elicit, in three groups: thiazide diuretics, loop diuretics and potassium-sparing diuretics (PSDs). In a previous article, we focused on the mechanism of action, pharmacodynamics, antihypertensive effects, adverse effects, interactions and contraindications of thiazide diuretics [4]. This review broadly discusses the clinical pharmacology of loop diuretics and PSDs, including the mineralocorticoid receptor antagonists (MRAs) and the epithelial Na⁺ channel (ENaC) blockers (Table 1).

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Article highlights.

- Loop diuretics reversibly inhibit the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ cotransporter in the apical membrane of epithelial cells of the thick ascending limb of Henle's loop. They are less effective than thiazide diuretics in lowering blood pressure and their effects on clinical outcomes in hypertensive patients remains unknown. Their major use is in edematous states in patients with heart failure (HF) and cirrhosis with ascites, being the preferred diuretics in patients with a GFR < 30 ml/min.
- Loop diuretics (furosemide, torsemide) present important differences in their pharmacodynamic/ pharmacokinetic properties.
- Mineralocorticoid receptor antagonists (spironolactone and eplerenone) competitively inhibit the binding of aldosterone to the mineralocorticoid receptors in the distal tubule and collecting duct cells and render them transcriptionally inactive. They represent a major advance in the treatment of resistant hypertension and hyperaldosteronism. In patients with congestive HF or post-myocardial infarction they reduce morbidity and mortality.
- Epithelial Na^+ channel blockers (amiloride, triamterene) directly block ENaC channels located in the luminal membrane of the principal cells of the distal tubule and collecting duct and produce weak natriuretic effects.
- Because the different diuretics inhibit Na^+ reabsorption at different tubular sites of the nephron, loop diuretics can be combined with thiazide diuretics and/or potassium-sparing diuretics (spironolactone, eplerenone, amiloride, triamterene). This *sequential nephron blockade* provides additive natriuretic and antihypertensive effects in patients with diuretic resistance. The combination of potassium-sparing diuretics with thiazides and/or loop diuretics reduces the risk of hypokalemia and hypomagnesemia and the risk of cardiac arrhythmias and sudden death in hypertensive patients.

This box summarizes key points contained in the article.

2. Loop diuretics

2.1 Mechanism of action

2.1.1 Renal effects

Loop diuretics are filtered at the glomerulus and reach their luminal site of action after being actively secreted via an organic acid transport mechanism in the proximal tubule. They reversibly inhibit the $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ co-transporter (encoded by the NKCC2 gene) in the apical membrane of epithelial cells of the thick ascending limb of Henle's loop after combining with its Cl^- site (Figure 1) [5,6]. Loop diuretics also block NKCC2 in the macula densa and, thus, inhibit the tubulo-glomerular feedback mechanism. The more the amount of diuretic reaching the site of action, the greater the response [2,5]. Thus, the diuretic excretion rate is a better reflection of the amount of diuretic that is able to interact with NKCC2.

Approximately 25% of the Na^+ load of the original filtrate is reabsorbed at the thick ascending limb of the Henle's loop. From this point, the urine flows into the distal convoluting tubule, where approximately 5% of the Na^+ load is transported via a $\text{Na}^+\text{-Cl}^-$ co-transporter sensitive to thiazide diuretics into the cortical interstitium. The distal segment of the distal convoluting tubule and the upper collecting duct reabsorb approximately 1 – 2% of the Na^+ load in exchange for K^+ and H^+ , which are excreted into the urine. By acting on the thick ascending limb, loop diuretics are the most powerful diuretics.

Loop diuretics reduce the reabsorption of NaCl, which indirectly increases K^+ excretion as they increase the delivery of filtered Na^+ to the distal and the collecting ducts, which, in turn, stimulates the aldosterone-sensitive $\text{Na}^+\text{-K}^+$ exchange mechanism (e.g., inwardly rectifying K^+ [ROMK1] and Na^+ channels in the luminal membrane coupled with basolateral $\text{Na}^+\text{-K}^+$ ATPases), facilitating the exchange of Na^+ by K^+ and H^+ , which are lost in the urine [2,6]. Cl^- leaves the cell via the basolateral Cl^- channels (ClC-K2) and the electroneutral K^+/Cl^- co-transporter. Because Cl^- but no HCO_3^- is lost in the urine, the plasma concentration of HCO_3^- increases as plasma volume is reduced.

The apical membrane of epithelial cells contains only K^+ channels, while the basolateral membrane contains channels for both K^+ and Cl^- , which results in a transepithelial potential difference of approximately 10 mV, that provides a driving force for paracellular absorption of mono- and divalent cations. Loop diuretics abolish this potential difference and inhibit the reabsorption of Na^+ , Cl^- , K^+ , Ca^{2+} and Mg^{2+} . However, loop diuretics decrease the excretion of uric acid.

The thick ascending limb of the Henle's loop is impermeable to water, so that the movement of Na^+ and Cl^- into the medullary interstitium without accompanying water increases the osmotic pressure at this level. In the presence of vasopressin, the hypertonicity of the medullary interstitium allows water reabsorption in the medullary collecting tubule, resulting in the excretion of concentrated urine. Loop diuretics inhibit NaCl transport in ascending limb of the loop of Henle and interfere with the mechanism that produces a hypertonic medullary interstitium reducing the gradient for water movement from the descending limb and the medullary collecting duct. As a result, they decrease the ability of the kidney to maximally concentrate urine. Thus, loop diuretics induce not only natriuresis but also diuresis, that is, they promote additional water loss in relation to Na^+ excretion.

2.1.2 Vascular effects

Loop diuretics interact with NKCC1, the only isoform of $\text{Na}^+\text{-K}^+\text{-2Cl}^-$ co-transporter in vascular smooth muscle cells (VSMC), hyperpolarize their membrane potential and suppress myogenic tone and contractions evoked by membrane depolarization, phenylephrine, angiotensin II and uridine triphosphate [7]. Intravenous (i.v.) administration of loop diuretics produces a rapid (within minutes) venodilator

Table 1. Classification of loop diuretics and PSDs.

Loop diuretics	Bumetanide Ethacrynic acid Furosemide Piretanide Torsemide	
PSDs	Mineralocorticoid receptor antagonists: Epithelial Na ⁺ channel blockers:	Spironolactone Eplerenone Amiloride triamterene

PSDs: Potassium-sparing agents.

effect, particularly in patients with pulmonary edema, which precedes its diuretic effect [2,8]. This venodilatation reduces venous return (preload), right atrial and pulmonary capillary wedge pressures. Additionally, loop diuretics tend to increase renal blood flow with a redistribution of the flow from the medulla to the cortex and within the cortex without increasing the glomerular filtration rate (GFR). This vasodilator effect is related to an increase in the renal synthesis and release of prostaglandins (PGE₂ in the medulla and PGI₂ in the glomeruli), a decrease in the responsiveness to vasoconstrictors (noradrenaline, angiotensin II) and in the release of nitric oxide or of endogenous ouabain-like natriuretic hormone and the opening of K⁺ channels in resistance arteries [9,10].

2.2 Pharmacodynamics

2.2.1 Antihypertensive effects

Loop diuretics decrease tubular Na⁺ re-absorption, produce diuresis and natriuresis, and reduce extracellular fluid and plasma volumes, cardiac output and systemic vascular resistances. In contrast to thiazide diuretics, loop diuretics present a sigmoidal relation between the natriuretic response and the amount of diuretic reaching their site of action, so that a maximally effective dose can completely block Na⁺ re-absorption. In healthy volunteers, an i.v. dose of 40 mg of furosemide, 20 mg of torsemide or 1 mg of bumetanide causes a maximal response, that is, the excretion of 200 – 250 mEq of Na⁺ in 3 – 4 l of urine over a time interval of 3 – 4 h [1]. Because loop diuretics must be filtered at the glomerulus to reach their site of action in the lumen of the tubuli, diseases that decrease GFR (i.e., CKD or HF) shift the dose curve to the right and downward, indicating a state of diuretic resistance, where the maximal natriuretic response is attenuated, and so higher doses are needed to produce the same level of diuresis [5].

Loop diuretics are less effective than thiazide diuretics in lowering BP. The best antihypertensive responses are observed in the elderly, in blacks (consistent with a more active NCCK2 co-transporter in the thick ascending limb) and in patients with HF or CKD, while the response in younger whites is less [8,11]. In a comparative study in black hypertensives, hydrochlorothiazide (HCTZ) produces a greater reduction in BP and in plasma potassium (0.26 mEq/l) than furosemide [12]. Moreover, twice-daily furosemide is less

effective than twice-daily HCTZ and once-daily chlorthalidone, but both drugs produce similar hypokalemia and hyperuricemia; however, furosemide exerts a more potent diuretic effect [13]. Nine trials evaluated the dose-related BP lowering efficacy of four loop diuretics (furosemide 40 – 60 mg, cicletanine 100 – 150 mg, piretanide 3 – 6 mg and etozolin 200 mg) in 460 patients with baseline systolic/diastolic blood pressure (SBP/DBP) of 162/103 mmHg for a mean duration of 8.8 weeks. The SBP/DBP lowering effect of loop diuretics is modest (7.9/4.4 mmHg) and is likely an overestimate due to the high risk of bias in the included studies [14]. There are no clinically meaningful differences in BP lowering or in withdrawals due to adverse effects and serum biochemical changes among the different drugs. Unfortunately, there are no outcome studies with loop diuretics. Intravenous furosemide or torsemide can be used in hypertensive crisis when fluid overload is present or when the intestinal absorption of the drug is decreased (e.g., in patients with congestive HF and reduced intestinal perfusion).

To exert an antihypertensive effect, loop diuretics must provide enough natriuresis to maintain persistent volume depletion. Furosemide and bumetanide present a short duration of action (~ 6 h), so that they cause an initial natriuresis, that is followed by a period of anti-natriuresis lasting up to 18 h/day when the drug is administered once daily. During this period of time, there is a post-diuretic Na⁺ re-absorption in the nephron (the *braking* phenomenon), an effect that can counteract the previous natriuresis, especially if Na⁺ intake is not restricted. This explains why furosemide is more effective when given in twice daily as compared to once daily [15]. This braking phenomenon can be prevented by increasing the frequency of dosing, avoiding the intake of Na⁺ at the end of the dosing intervals, when most part of it will be retained, and using long-acting loop diuretics, that is, torsemide that can be administered once daily [1,2,5]. The braking phenomenon results from glomerular hemodynamic changes and from adaptative changes in the distal tubuli mediated, in part, by activation of the renin-angiotensin-aldosterone-system (RAAS) and sympathetic tone [2,5,9,15]. Loop diuretics increase the release of renin by several mechanisms, including the decrease of intravascular volume, which activates renal baroreceptors and β₁-adrenoceptors, the hyponatremia and the direct stimulation of renin release by blocking Na⁺ transport by the macula densa and the upregulation of renin gene expression in the kidney [2,5,15]. Activation of the RAAS and sympathetic tone causes Na⁺ and water retention and vasoconstriction, effects that partly counteract the BP reduction, facilitates cardiovascular (CV) remodeling and play a key role in HF progression [9,15,16]. This explains why the co-administration of a loop diuretic with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II-receptor blocker (ARB) inhibits the increase in peripheral vascular resistances and increases the antihypertensive response.

During chronic loop diuretic administration, the distal nephron is exposed to a high Na⁺ load, that causes an aldosterone-induced hypertrophy of distal convoluted tubule

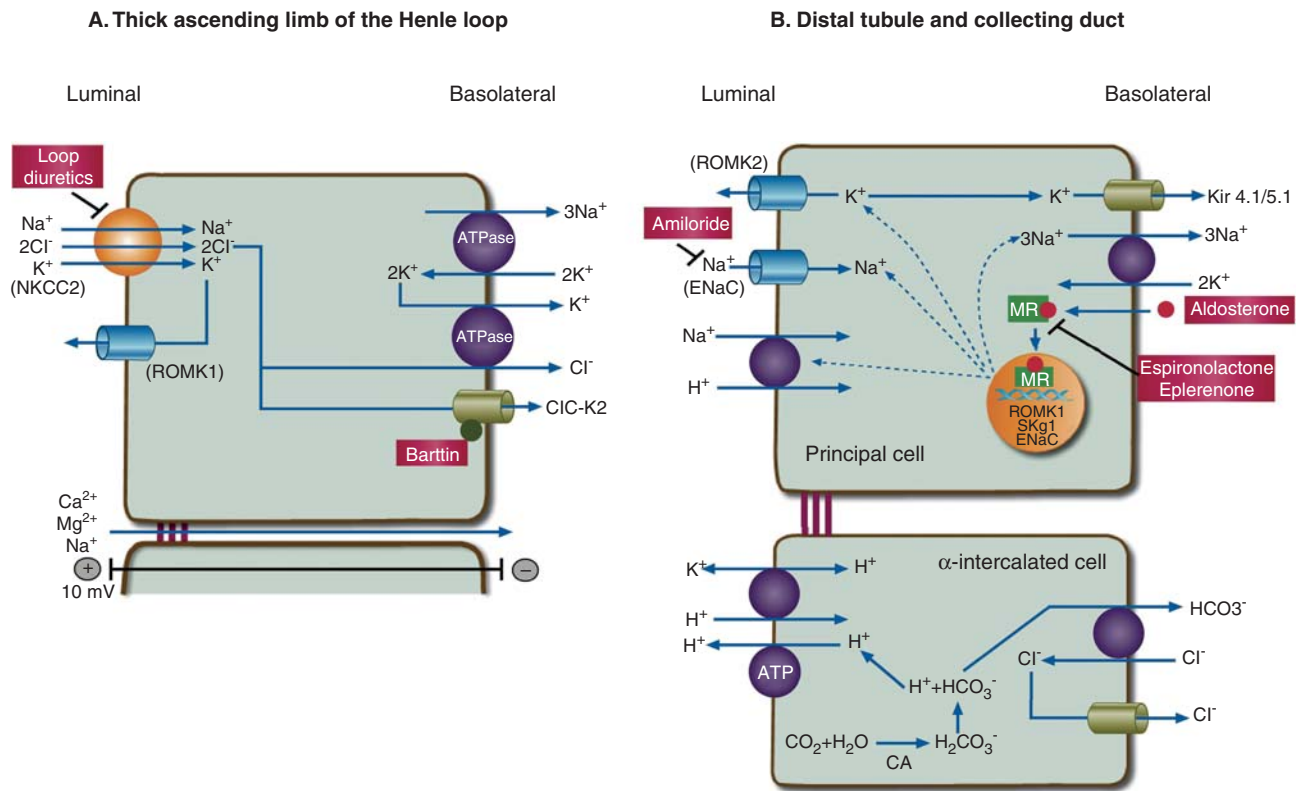


Figure 1. A. Mechanism of action of loop diuretics in the thick ascending limb of the Henle loop. Re-absorption of NaCl in the thick ascending limb of the Henle loop is mediated via the Na⁺-K⁺-2Cl⁻ (NKCC2) co-transporter. Its activity is driven by the low intracellular Na⁺ and Cl⁻ concentrations produced by the basolateral Na⁺-K⁺ ATPase pump, the K⁺/Cl⁻ co-transporter and the Cl⁻ channel (CIC-Kb). **B.** Electrolyte transport in the late distal tubule and collecting duct. Re-absorption of Na⁺ occurs via the amiloride-sensitive epithelial Na⁺ channel (ENaC) that is coupled to K⁺ and H⁺ secretion. Aldosterone increases the activity of ENaC and Na⁺-K⁺ ATPase, which increases Na⁺ re-absorption and K⁺ and H⁺ secretion, and other elements of the Na⁺ transport machinery. Aldosterone also stimulates secretion of H⁺ in exchange for Na⁺ in the intercalated cells of the cortical collecting tubules via the H⁺-ATPase and H⁺-Na⁺-ATPase, thus regulating plasma HCO₃⁻ levels. Aldosterone antagonists (eplerenone, spironolactone) competitively inhibit the binding of aldosterone to the MR, while amiloride and triamterene directly block ENaC channels, and thereby Na⁺ re-absorption, in the luminal membrane of the principal cells of the distal tubule and collecting duct. See text for details.

Aldo: Aldosterone; Barttin: β-subunit of the CIC-Kb channels; CA: Carbonic anhydrase; ENaC: Epithelial sodium channel; MR: Mineralocorticoid receptor; ROMK1: Apical ATP-dependent K⁺ channel; Sgk: Serum and glucocorticoid-induced kinase.

cells, and increases re-absorption of Na⁺ delivered from more proximal locations, so that the overall diuresis decreases. Thiazide diuretics inhibit distal tubular hypertrophy and their combination with loop diuretics results in substantial natriuresis [2,9,15-17].

2.2.2 Other clinical uses

Loop diuretics decrease blood volume, venous pressure and capillary hydrostatic pressure, which reduce net capillary fluid filtration and edema associated with CKD, nephrotic syndrome and chronic liver disease and ascites. Loop diuretics are the preferred diuretics in patients with a GFR < 30 ml/min/1.73 m² (CKD stages 4 – 5), where thiazide diuretics are expected to have a limited effect [2,8,18].

In patients with HF, loop diuretics, added to standard therapy, including ACEIs/ARBs, β-blockers and MRAs, are recommended in patients with clinical signs and symptoms of pulmonary and systemic venous congestion, especially when renal perfusion is impaired [19]. Loop diuretics are the preferred diuretics because in comparison with thiazides, they produce a relatively greater urine volume and relatively less loss of Na⁺ and a rapid venodilator effect that reduces the preload, their effect is maintained in patients with CKD and present a clear dose-response curve (i.e., increasing doses increase diuretic responses). The dose requirement must be tailored to the individual patient's needs and requires careful clinical monitoring.

Because the different diuretics inhibit Na⁺ re-absorption at different tubular sites of the nephron, loop diuretics can be combined with thiazide diuretics and/or PSDs. This *sequential*

nephron blockade permits to obtain the desired final diuretic effect and a better control of BP. In patients with resistant peripheral edema, the combination of a loop and a thiazide (e.g., bendroflumethiazide) or thiazide-like diuretic (metolazone) may be needed to achieve an adequate diuresis [19]. This combination requires careful monitoring of fluid status and serum electrolytes to avoid dehydration, hypokalemia, hyponatremia, hypovolemia or renal dysfunction.

Intravenous furosemide or torsemide can be used in the emergency treatment of severe hypercalcemia or hyperkalemia.

2.2.3 Differences between furosemide and torsemide

Torsemide differs from other loop diuretics such as furosemide in its pharmacodynamic/pharmacokinetic properties (next Section). On an mg-to-mg basis, the diuretic, natriuretic and chloruretic effects of torsemide are approximately eight times greater than for furosemide [20]. Additionally, torsemide, but not furosemide, inhibits angiotensin II-induced vasoconstriction and vascular growth-promoting activity [21], aldosterone secretion and the binding of aldosterone to its receptor in the cytoplasmic fraction of rat kidney [22]. Inhibition of aldosterone secretion could reduce kaliuresis, and that may explain why torsemide causes less kaliuresis than does furosemide at doses that cause an equivalent level of natriuresis in patients with chronic HF [23]. Furthermore, torsemide, but not furosemide, significantly reduces cardiac synthesis and deposition of collagen type I fibers in biopsies from hypertensive patients with symptomatic chronic HF [24] and attenuates cardiac sympathetic nerve activity and left ventricular (LV) remodeling in patients with chronic HF as compared with furosemide [24,25].

Torsemide presents a more rapid, greater and less variable oral absorption than that of furosemide in patients with chronic HF [26]. It has been hypothesized that these pharmacokinetic differences can be translated into an improved tolerability, and better outcomes (improved functional class and quality of life, reduced risk of HF readmissions and CV death) with long-acting (torsemide) as to short-acting (furosemide) loop diuretics [23,27,28]. A very recent meta-analysis of six trials although demonstrating remarkable heterogeneity, suggests trends toward improved functional status and mortality with torsemide compared with furosemide [29]. However, there are no clinical studies that have compared the efficacy of torsemide versus furosemide in patients with acute HF.

2.3 Pharmacokinetics

There are clinically important differences in the pharmacokinetic properties of loop diuretics [3,5]. All are rapidly absorbed from the gastrointestinal tract, reaching their peak effect after 1 – 1.5 h (10 – 30 min when given i.v.). Furosemide, the most widely used loop diuretic, presents a marked inter-individual bioavailability (10 – 90%, mean 40%), which increases with generic products and is reduced by food; thus, it should be taken with an empty stomach. In

hypertensive patients, the effects of furosemide reach steady-state effects after 4 – 6 weeks. In contrast, oral absorption of bumetanide and torsemide is almost complete both in healthy individuals and in patients with HF where gut edema is present, so that their effects are more predictable than those of furosemide [5]. Loop diuretics bind extensively to plasma proteins (> 95%), so that they enter the urine primarily by tubular secretion in the proximal tubule, while their delivery to the tubule by glomerular filtration is limited. Almost 50% of the dose of furosemide is excreted unchanged in urine; the other 50% is conjugated with glucuronic acid in the kidneys [1,5]. Thus, the pharmacokinetics of furosemide appears to depend more on kidney function than on liver disease. In patients with renal insufficiency, oral bioavailability of furosemide decreases and plasma half-life increases because both urinary excretion and renal conjugation decrease [1,5,17].

Bumetanide and torsemide undergo hepatic metabolism (50 and 80%, respectively), so their half-lives are prolonged in patients with hepatic insufficiency, but not with renal insufficiency [1,5]. Patients with cirrhosis exhibit a decrease in nonrenal clearance and an increase in bioavailability, volume of distribution, renal clearance, elimination half-life and percentage of the dose excreted into the urine. These pharmacokinetic changes compensate the shift of the dose-response curve to the right, so that in patients with cirrhosis there are no significant differences in natriuresis [1,5,30]. As expected, renal excretion of torsemide and its metabolites is significantly retarded in patients with CKD.

2.4 Special populations

2.4.1 Heart failure

In patients with HF and preserved renal function, the delivery of loop diuretics to the tubular fluid is normal. These patients present gut wall edema that slows drug absorption and delays the time to peak urinary concentrations of the diuretic (≥ 4 h), but the total drug absorption is unchanged [1,5,26,31]. However, in chronic HF the maximal natriuretic response of loop diuretics is reduced due to the decrease in renal blood flow and GFR and neurohumoral activation [1,5,26]. Thus, these patients do not need higher doses, but it may be necessary to administer moderate doses of loop diuretics more frequently (or even i.v.) in patients on standard therapy, including RAAS inhibitors, which help to maintain potassium and magnesium plasma levels, and β blockers [17,19]. In patients with insufficient response or diuretic resistance, the combination of loop diuretics with metolazone may be needed to achieve an adequate diuresis [5,19].

2.4.2 Renal failure

All loop diuretics have a diminished natriuretic response in patients with CKD or nephrotic syndrome [1,5,18]. Factors limiting the natriuretic response in patients with CKD do not include a reduction in bioavailability but an enhanced

Na⁺ re-absorption in downstream segments of the nephron and a reduced renal excretion of loop diuretics occurring in parallel with the decrease in GFR [1,5]. Indeed, patients with a creatinine clearance < 15 ml/min deliver only 15 – 20% as much loop diuretics into the tubular fluid as a healthy volunteer [1,18]. The reduced activity of the organic acid transporter in the proximal tubule is due to raised levels of endogenous organic anions that interfere with loop diuretic secretion in these patients. Thus, higher blood levels are required to increase tubular delivery sufficient to prompt a diuresis. In the nephrotic syndrome, two factors can reduce the amount of unbound-active diuretic available at the site of action: an inadequate secretion to the tubule lumen and drug binding to albumin in the tubular fluid [1,5,32]. Additionally, these patients may present a decrease in drug effects due to increased proximal or distal re-absorption of Na⁺. Thus, diuretic doses two to three times greater than normal are needed to attain an effective amount of diuretic in the tubular lumen and a normal diuretic response [18,32,33].

Strategies to improve loop diuretic response in these patients include appropriate changes in the dosing and/or frequency of administration of the drug, the coadministration of a thiazide diuretic to inhibit downstream Na⁺ re-absorption, reducing albumin renal excretion (with administration of an ACEI/ARB and appropriate limitation of protein intake), restricting dietary Na⁺ intake and considering the use of a nonrenally metabolized diuretic, like torsemide, rather than furosemide.

2.4.3 Cirrhosis

Cirrhotic patients should receive loop diuretics only when spironolactone are ineffective. Unless they have diminished renal function, normal amounts of loop diuretics are delivered into the urine [5,32]. In patients with hepatic disease, the plasma half-lives of bumetanide and torsemide are prolonged and more drug reaches the tubular fluid, an effect that can paradoxically enhance response [1]. Therefore, these patients do not need higher doses, unless CKD is present.

2.5 Adverse reactions

The review of randomized clinical trials (RCTs) does not provide a good estimate of the incidence of adverse effects of loop diuretics in hypertensive patients because of the short duration of the trials and the lack of reporting of adverse effects in many of them [14]. Additionally, there are no outcome data with loop diuretics in this population.

Loop diuretics can produce different adverse effects:

- a) *Hydroelectrolyte disturbances*: dehydration, hypovolemia, hypokalemia, hypomagnesemia, hyponatremia, hypochloremic alkalosis and hypocalcemia. Reduction or discontinuation in the diuretic dose, Na⁺ intake and, occasionally, restriction of water intake, can correct hyponatremia. Similarly, hypovolemia,
- b) *Cardiovascular*: excessively rapid mobilization of edema, particularly in elderly patients, may give rise to sudden changes in CV pressure–flow relationships leading to postural hypotension and renal dysfunction following initiation of ACEI/ARB therapy. The risk of hypokalemia-induced arrhythmias increases in patients taking digoxin or with LV hypertrophy, coronary artery disease, HF or acute myocardial infarction. A retrospective analysis of the *Studies Of Left Ventricular Dysfunction* (SOLVD) shows that in patients with moderate or severe LV dysfunction the use of non-PSDs (including furosemide) is associated with an increased risk of hospitalization or death for progression of chronic HF, and increased CV and all cause mortality when compared with no diuretic or combination therapy (i.e., combination of a PSD with a non-PSD) [34]. However, the risk of hypokalemia-induced arrhythmias in hypertensive patients treated with loop diuretics is uncertain.

Loop diuretics activate the RAAS and increase the sympathetic tone. This neurohumoral activation facilitates CV remodeling and plays a key role in HF progression [9,16].

Hypokalemia (serum potassium < 3.5 mEq/l) and hypomagnesemia (< 1.4 mEq/l) cause symptoms (fatigue, tremor, muscle cramps, constipation and anorexia), electrocardiogram abnormalities and cardiac arrhythmias. In the doses used for mild hypertension (furosemide 20 mg twice daily, torsemide 5 – 10 mg once daily), hypokalemia is limited and possibly less than with HCTZ 25 – 50 mg/day. However, the risk of hypokalemia increases with the dose, in elderly and polymedicated patients and in patients with renal or HF. Hypokalemia can be managed with potassium supplemental or better, with a PSD. Concurrent ACEI/ARB therapy also counters hypokalemia by an anti-aldosterone effect. Normalization of hypokalemia and hypomagnesemia exert beneficial effects on co-existing electrolyte or neuromuscular symptoms, BP control, glucose intolerance, arrhythmia development and diuretic tolerance.

Thus, in patients with HF, loop diuretics should be used only in combination with a RAAS inhibitor and a β blocker.

- c) *Gastrointestinal*: anorexia, nausea, gastric irritation, constipation.
- d) *Central*: dizziness, vertigo, paresthesia, headache.
- e) *Metabolic adverse effects*: they are similar to those described for thiazide diuretics [4]. However, because there are no large, long-term, prospective studies on the effects of loop diuretics on insulin sensitivity, glucose tolerance or plasma lipid profile, it is uncertain whether loop diuretics cause less metabolic disturbances than do thiazide diuretics in equipotent doses in hypertensive patients [14]. Loop diuretics can increase serum urate concentrations due to an increased absorption in the proximal tubuli secondary to extracellular volume contraction and competition with uric acid for renal tubular secretion as they use the same organic acid transport pathway [1,2].
- f) *Other*: photosensitive skin eruptions (furosemide), myalgias, blood dyscrasias and rashes. Allergic interstitial nephritis may develop abruptly or some months after beginning therapy with furosemide. Reversible ototoxicity (tinnitus, vertigo, deafness) due to inhibition of NKCC2 in the basolateral membrane of the stria vascularis of the inner ear may appear at doses much higher than those needed to produce diuresis. Ototoxicity is greater with ethacrynic acid, so that this drug is reserved for patients who develop allergic reactions to other loop diuretics.

Urine output, serum and urine electrolyte determinations, serum glucose and creatinine levels and BP should be monitored during chronic treatment, particularly in patients with cardiac disease, diabetes, renal or hepatic impairment and in elderly patients. Loop diuretics should not be administered i.v. if serum electrolytes cannot be monitored.

Furosemide and bumetanide cross the placental barrier and are excreted in breast milk; thus, they should be avoided in pregnancy and breast-feeding (Pregnancy Category C). Torsemide is relatively safe in pregnancy (Pregnancy Category B).

2.6 Drug interactions

Loop diuretics can enhance the effects of other antihypertensives and increase the risk of postural hypotension when coadministered with alcohol, opioids and barbiturates, tricyclic antidepressants, neuroleptics or baclofen. Volume depletion and hyponatremia resulting from excessive diuresis increase the risk of hypotension and deterioration in renal function when loop diuretics are combined with an ACEI and an ARB [3,8,35], so that an interruption or reduction in the dosage of the diuretic, ACEI or ARB may be necessary.

Nonsteroidal anti-inflammatory drugs (NSAIDs) attenuate the natriuretic and vasodilator effects of loop diuretics by inhibiting the synthesis of renal vasodilatory prostaglandins

and causing Na^+ retention and blood urea nitrogen (BUN) and serum creatinine and K^+ levels [3,9]. Rheumatic patients receiving high doses of aspirin and loop diuretics may experience salicylate toxicity because of competitive renal excretory sites. Glucocorticoids, estrogen-containing oral contraceptives, sucralfate and bile acid sequestrants (cholestyramine and colestipol) also inhibit the diuretic and antihypertensive effects. Thus, the intake of loop diuretics and resins or sucralfate should be separated by at least 2 h.

Loop diuretics do not alter blood digoxin levels. However, diuretic-induced hypokalemia increases the risk of digitalis-induced arrhythmias and of polymorphic ventricular tachycardia (torsades de pointes) when given with drugs that prolong the QT interval of the ECG (e.g., class IA and III antiarrhythmics, phenothiazines, antipsychotics and some macrolides and antihistamines). The risk of hypokalemia increases when loop diuretics are coadministered with β -agonists (terbutaline), ACTH, corticosteroids, xanthines, acetazolamide, carbenoxolone, reboxetine, theophylline and amphotericin B and the risk of hyponatremia when coadministered with carbamazepine and amphotericin [3]. The combination of loop diuretics with β -blockers is not recommended in patients with diabetes or metabolic syndrome who are prone to develop new-onset diabetes [8].

Loop diuretics displace warfarin from plasma proteins and a reduction in warfarin dose may be required in patients receiving both drugs [3,35]. Loop diuretics also increase the risk of nephrotoxicity when coadministered with other nephrotoxic drugs (i.e., NSAIDs, aminoglycoside antibiotics, amphotericin B, some cephalosporins) especially in patients with impaired renal function. There is a risk of ototoxic and nephrotoxic effects when cisplatin and loop diuretics are given concomitantly, particularly if the diuretic is given at high doses and with negative fluid balance. Phenytoin decreases absorption of furosemide and reduces its peak plasma levels and its antihypertensive effect. Methotrexate undergoes significant renal tubular secretion and may reduce the effect of furosemide. Concomitant use of cyclosporin, which impairs renal urate excretion, and furosemide increase the risk of gouty arthritis. Loop diuretics can antagonize the skeletal muscle relaxing effect of tubocurarine and may enhance the action of succinylcholine. In a large population-based study, the use of loop diuretics in elderly patients significantly increases the risk of hospitalization for Li^+ toxicity [36].

2.7 Contraindications and precautions

Furosemide and bumetanide are contraindicated in patients allergic to sulfonamides as is torsemide in those allergic to sulfonylureas. Loop diuretics should not be given in patients with hypokalemia, severe hyponatremia, hypotension, azotemia and/or oliguria. Loop diuretics should also be avoided on the day of surgery because of potential adverse interaction with surgery-dependent fluid depletion [13]. Doses of loop diuretics should be individually tailored, according to the renal/hepatic functional status of the patient, to avoid the

risk of dehydration and renal insufficiency and to prevent the recurrence of volume overload.

3. Potassium-sparing diuretics

3.1 Mechanism of action

In the kidney, aldosterone binds to intracytoplasmic mineralocorticoid receptors (MRs) located in the principal cells of the distal tubules and collecting ducts of the nephron. The aldosterone-MR complex is translocated to the nucleus, where it binds to specific hormone response elements in the regulatory region of target gene promoters, modulating the synthesis of a number of proteins involved in transepithelial Na^+ transport, including the α -subunit of amiloride-sensitive apical ENaC, the Na^+/K^+ -ATPase, the renal K^+ channel (ROMK2) and the serum and glucocorticoid-induced kinase 1 (sgk1). Sgk1 enhances the density of apical ENaC channels through direct phosphorylation and inhibition of ubiquitin ligase Nedd4-2-mediated internalization of the channels. Furthermore, effects of Sgk1 on ENaC and Na^+/K^+ -ATPase also increase the driving force for K^+ secretion through ROMK2 [37,38].

As a result, aldosterone increases (Figure 1B): i) the expression and activity (open probability) of amiloride-sensitive apical ENaC, which mediate the electrogenic Na^+ absorption and drive secondary K^+ and H^+ secretion; ii) the activity of K^+ (ROMK2) channels increasing the secretion of K^+ into the tubular lumen; iii) the synthesis and activity of the basolateral Na^+/K^+ -ATPase, which results in re-absorption of Na^+ and water, and secretes K^+ into the lumen. Additionally, in the intercalated cells of the cortical collecting tubules aldosterone facilitates the secretion of H^+ via the apical H^+ -ATPase and H^+/K^+ exchanger and facilitates the absorption of bicarbonate via the basolateral $\text{Cl}^-/\text{HCO}_3^-$ exchanger. Thus, aldosterone is responsible for the renal re-absorption of 1 – 2% of Na^+ filtered at the glomerulus and promotes Na^+ and water retention and increases K^+ and H^+ secretion and water retention. Cl^- is reabsorbed with Na^+ to maintain the system's electrochemical balance. Na^+ exits cells across the basolateral membrane to the interstitial fluid via the ubiquitous Na^+/K^+ ATPase, which provides the driving force for Na^+ transport. Basolateral K^+ channels (Kir4.1 and Kir5.1) participate in generating cell membrane potential and in K^+ recycling, while apical K^+ channels, mainly ROMK2, are responsible for K^+ secretion.

Additionally, aldosterone exerts deleterious cardiac, vascular and renal effects, including endothelial dysfunction, K^+ and Mg^{2+} depletion, sympathetic activation, induces cardiac hypertrophy, increases cardiac, renal and vascular collagen synthesis, Na^+ influx in VSMC and pressor responses to catecholamines and angiotensin II, decreases arterial compliance, increases oxidative stress and induces a pro-inflammatory and pro-arrhythmic effects [37-39]. The deleterious CV effects of aldosterone require concomitant pathophysiological conditions such as a high salt diet, increased oxidative stress or inflammation [38].

3.1.1 Mineralocorticoid receptor antagonists

Spironolactone and eplerenone competitively inhibit the binding of aldosterone to the MR in the distal tubule and collecting duct cells and render it transcriptionally inactive. They inhibit aldosterone-induced synthesis of ENaC and, consequently, Na^+/K^+ exchange, leading to natriuresis and K^+ retention. They also block other deleterious effects of aldosterone (including endothelial dysfunction, the increase in sympathetic tone and the vasoconstrictor response to angiotensin II, cardiac, renal and vascular remodeling) and exhibit anti-arrhythmic effects. Spironolactone is a nonselective MRA that also exerts anti-androgenic and progesterone-like effects [39]. Eplerenone has 60% of the antagonist potency of spironolactone but is a more specific blocker of the MR, presenting up to a 500-fold lower affinity for androgen and progesterone receptors than spironolactone. Therefore, eplerenone is the alternative in patients with spironolactone-induced gynecomastia and sexual dysfunction [40].

3.1.2 Potassium-sparing agents

Amiloride and triamterene are filtered at the glomerulus and secreted by the organic cation secretory pathway into the proximal tubule [41]. They directly block ENaC channels located in the luminal membrane of the principal cells of the distal tubule and collecting duct, perhaps by competing with Na^+ for negative charges within the channel pore. The reduction in Na^+ re-absorption hyperpolarizes the apical membrane of the tubule and reduces the electrochemical gradient for K^+ secretion from the principal cell and H^+ secretion via the H^+ -ATPase from the intercalated cell. Additionally, the reduction in K^+ secretion decreases H^+ secretion via K^+/H^+ ATPase, which can cause metabolic acidosis. The net effect is an increase in Na^+ excretion and a decrease in K^+ and H^+ excretion. However, in contrast to MRA, the K^+ retention induced by amiloride and triamterene is independent of aldosterone. At high doses, both drugs also inhibit the Na^+/H^+ (and amiloride the $\text{Na}^+/\text{Ca}^{2+}$) exchanger [41].

3.2 Pharmacodynamics

3.2.1 Mineralocorticoid receptor antagonists

Aldosterone acts as a downstream effector of the RAAS and an increase in aldosterone:renin ratio has been identified in hypertensive patients, particularly in those with resistant hypertension [42-45]. In these patients, there is evidence of intravascular volume expansion, particularly in men and the significant correlation between 24-h urinary aldosterone levels and cortisol excretion suggests that a common stimulus, such as corticotropin, may underlie the aldosterone excess in patients with resistant hypertension [45].

MRAs are indicated in the treatment of primary and secondary hyperaldosteronism, in patients with resistant hypertension who are receiving multidrug antihypertensive regimens and in patients with congestive HF or post-myocardial infarction.

3.2.1.1 Primary hyperaldosteronism

Patients with primary hyperaldosteronism present hypertension, LV hypertrophy and more CV events (stroke, myocardial infarction, atrial fibrillation and death) than in those with normal aldosterone levels [40]. Spironolactone is the drug of choice in the treatment of primary hyperaldosteronism, including a short-term preoperative treatment and a long-term maintenance therapy in patients with adrenal adenomas who have poor operative risks or who decline surgery and in patients with bilateral (idiopathic adrenal hyperplasia or idiopathic bilateral adenoma) or unilateral disease who are unable to undergo adrenalectomy [46].

Spironolactone lowers BP to a similar extent in hypertensive patients with and without primary aldosteronism, although a higher dose is required in those with primary aldosteronism [46,47]. Treatment with spironolactone reduces the rate of CV and renal complications, decreases LV hypertrophy and urinary protein excretion, and corrects abnormalities of glucose metabolism (hypersinsulinemia and insulin resistance) [46]. The long-term effects of spironolactone on CV outcomes (comprising myocardial infarction, stroke, any type of revascularization procedure and sustained arrhythmias) were studied in patients with primary aldosteronism followed-up for a mean of 7.4 years after treatment with adrenalectomy or spironolactone [48]. BP and CV outcomes during follow-up were comparable in the primary aldosteronism and essential hypertension groups, indicating that adrenalectomy and spironolactone are equally effective in the prevention of CV outcomes.

Two recent studies compare the antihypertensive efficacy of eplerenone and spironolactone in patients with idiopathic hyperaldosteronism. In one study, spironolactone (50 – 400 mg/day) and eplerenone (50 – 200 mg/day) produce a similar reduction in BP [49], while in another study spironolactone (75 – 225 mg/day) is significantly superior to eplerenone (100 – 300 mg/day), but more patients randomized to spironolactone develop gynecomastia and mastodynia [50].

3.2.1.2 Resistant hypertension

Sodium retention and volume expansion, mediated in part by aldosterone, are prominent features in low-renin hypertension. Spironolactone and eplerenone are particularly effective antihypertensive agents in patients with low-renin or with resistant hypertension [51]. They are also effective in reducing BP in hypertensives treated with RAAS inhibitors (ACEIs or ARBs) with elevated aldosterone plasma levels possibly reflecting an undetected aldosteronism or that RAAS inhibitors incompletely suppressed aldosterone secretion (aldosterone escape) [52].

In patients with resistant hypertension, after 1 month of treatment, spironolactone reduces SBP/DBP by 26/10 mmHg [44]. Adding a low dose of spironolactone (12.5 – 25 mg/day) to a multidrug regimen that includes a diuretic and an ACEI or ARB in subjects with resistant hypertension with and without primary aldosteronism produces a mean decrease in SBP/DBP 21/10 and 25/12 mmHg at 6 weeks and 6 months of treatment, respectively [53]. The BP reduction is similar in subjects with and

without primary aldosteronism and is additive to the use of ACE inhibitors, ARBs and diuretics. In another study, the addition of spironolactone (25 – 50 mg) in patients with resistant hypertension treated with an angiotensin-blocking drug in addition to other therapies produces a mean fall in SBP/DBP of 21.7/8.5 mmHg. In two patients spironolactone had to be discontinued because of a rise of serum K⁺ to > 6.0 mM/l, whereas overall the mean increase in serum K⁺ was 0.3 mM/l [42].

In the *Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm* patients with uncontrolled hypertension receiving a mean of approximately three other drugs, the addition of spironolactone (mean dose of 25 mg/day) reduces SBP/DBP by 21.9/9.5 mmHg, a reduction largely unaffected by age, sex and diabetic status [43]. Spironolactone is well tolerated and only 6% of participants discontinued the drug because of adverse effects. The most frequent adverse events are gynecomastia or breast discomfort and biochemical abnormalities (principally hyperkalemia), which are recorded in 6 and 2% of participants, respectively. In a meta-analysis, including five crossover studies and one RCT, spironolactone decreases SBP/DBP by 20/6.7 mmHg, but it appears that doses of > 50 mg/day do not produce further reductions in either SBP or DBP [54]. All these results clearly support the use of spironolactone in uncontrolled hypertension. Unfortunately, the effect of spironolactone on clinical outcomes in hypertensive patients remains unknown.

Eplerenone (50 mg/day) is effective in treating hypertension, either as monotherapy or in combination with other antihypertensives [40,55]. In a 8-week trial, in 417 patients with mild to moderate hypertension uncontrolled with an ACEI or an ARB, eplerenone (25, 50 and 200 mg b.i.d.) and spironolactone (50, 100 or 400 mg od) decrease dose-dependently seated SBP/DBP during a 24-h period [51]. However, the mg-for-mg BP-lowering effect of eplerenone is less than that of spironolactone, so that eplerenone (100 mg) reduced BP by 75% compared with spironolactone (100 mg). In another study, eplerenone (50 mg/day) is superior to placebo and losartan in all patients combined and in black patients, and is superior to placebo in white patients. Eplerenone is as effective as losartan in reducing SBP/DBP in high-renin patients and in patients with differing baseline levels of aldosterone, but it is more effective than losartan in black patients [56]. Furthermore, after 8 weeks of therapy, eplerenone is more effective than losartan in reducing SBP/DBP in patients with low-renin hypertension. After 16 weeks of therapy, significantly fewer eplerenone-treated patients than losartan-treated patients (32.5 vs 55.6%) require add-on HCTZ as allowed per protocol for BP control [57]. Eplerenone consistently reduces BP regardless of baseline active plasma renin levels, whereas losartan reduces BP more effectively in patients with higher baseline active renin levels. Moreover, in comparative trials, eplerenone is as effective as amlodipine or enalapril in lowering SBP [40].

In the 4E study, eplerenone (200 mg/day) is as effective as enalapril (40 mg/day) in lowering LV hypertrophy and SBP [58], but the combination eplerenone/enalapril is more effective than eplerenone alone.

Aldosterone *per se* is an essential link between hypertension and the development of vascular remodeling and hypertensive nephropathy [59]. Spironolactone and eplerenone added to an ACEI (or an ARB) reduce albuminuria in patients with diabetic nephropathy or other proteinuric diseases without producing significant increases in hyperkalemia [40,46,59-62]. This finding suggests that MRAs reduce intraglomerular pressure, thereby protecting the kidney in the long term. Indeed, eplerenone is more effective than amlodipine, enalapril and losartan in decreasing urinary albumin excretion [40,56]. A meta-analysis of 11 RCTs found that MRAs reduce proteinuria in patients with CKD already on ACEI and ARB but increase the risk of hyperkalemia [63]. However, long-term effects of MRAs on renal outcomes, mortality and safety are unknown.

3.2.1.3 Heart failure

Spironolactone and eplerenone are recommended for all patients with persisting symptoms (NYHA class II – IV) and an LV ejection fraction $\leq 35\%$, despite treatment with an ACEI (or an ARB) and a β blocker, to reduce the risk of HF hospitalization and the risk of premature death [19,39]. They also improve diastolic function in essential hypertension [64], prevent or reverse myocardial remodeling (hypertrophy and fibrosis) in patients with congestive heart or post-myocardial infarction, exert anti-arrhythmic properties [65], prevent atrial fibrillation in patients with hypertension or HF, and reduce sudden cardiac death and total mortality post-myocardial infarction [13,39,66,67].

3.2.1.4 Liver cirrhosis

Spironolactone is indicated in patients with cirrhosis and ascites, in whom secondary hyperaldosteronism is present, and hypokalemia is detrimental [68].

3.2.2 Amiloride and triamterene

In monotherapy, both drugs produce weak natriuretic effects and are relatively ineffective in lowering BP. Their natriuretic effect is greater in patients with primary or secondary (e.g., with cirrhosis and ascites or HF) hyperaldosteronism. Thus, they are primarily used in combination with thiazide or loop diuretics, either to prevent the urinary loss of K^+ and Mg^{2+} or to increase the net diuresis in patients with low-renin hypertension, resistant hypertension or congestive HF or refractory edema [1,2,17]. Amiloride can provide an additional reduction in BP in blacks with low-renin hypertension already receiving conventional antihypertensive therapy [69]. Amiloride is also effective in patients with polyuria and polydipsia due to Li^+ -induced nephrogenic diabetes insipidus. The resistance to ADH in these patients appears to result from Li^+ accumulation in the collecting tubule cells through the ENaC channels of the luminal membrane. Amiloride is also

indicated in patients with Liddle syndrome and in patients with some ENaC mutations [70,71].

3.3 Pharmacokinetics

Spironolactone and eplerenone are well absorbed in the gastrointestinal tract (oral bioavailability 90 and 69%, respectively) and bind to plasma proteins (90 and 50%, respectively) (Table 2). Spironolactone presents a half-life of 1.4 h and is rapidly and extensively metabolized to active metabolites (7- α -thiomethyl-spironolactone and canrenone) with a longer half-life (16 – 35 h for canrenone) [3,47]. These active metabolites explain why its onset of action is slow (peak response after 48 h) and steady-state effects are reached 6 weeks after initiation of the treatment. The slow clearance of the active metabolites also explain why the duration of the natriuretic and antikaliuretic effects differ, the latter often persisting for several days after drug discontinuation. Spironolactone (once daily or in alternate days) remains effective in patients with CKD, but patients must be monitored carefully for the development of hyperkalemia. Eplerenone presents a shorter half-life (4 – 6 h) and it is rapidly metabolized in the liver via CYP3A4, but has no active metabolites. Its pharmacokinetics is not altered in the elderly or in patients with renal or hepatic insufficiency [40,47,72]. Because spironolactone and eplerenone do not rely on glomerular filtration or tubular secretion to reach its site of action in the lumen tubuli they are effective even in patients with advanced CKD.

Amiloride presents a low oral bioavailability, is not metabolized in the liver but is excreted unchanged in the urine, so that CKD prolongs its half-life, while hepatic insufficiency has little effect on its pharmacokinetics [47]. Triamterene is extensively metabolized in the liver and the drug (50%) and its active metabolite (4-hydroxytriamterene sulfate) are excreted in the urine. The amount of metabolite reaching the tubule decreases in hepatic insufficiency. In patients with CKD, both drugs have progressively limited access to their site of action and, therefore, became less effective.

3.4 Adverse effects

PSDs produce hyperkalemia, worsening renal function, metabolic acidosis, hypotension, dizziness, headache, nausea, flatulence, rash and flu-like symptoms (e.g., fever, chills and unusual tiredness). Spironolactone also produces diarrhea, gastritis, gastric bleeding/ulcers, headache and drowsiness, and because of its progestogenic and anti-androgenic adverse effects, gynecomastia, impotence, decreased libido, menstrual irregularities and breast tenderness [47,73]. Eplerenone can replace spironolactone in patients who develop these sexual adverse effects [40]. Because the incidence of gynecomasty is dose-related, a small dose of a thiazide diuretic can be added to avoid the use of higher doses of spironolactone. Triamterene causes folic acid depletion and kidney calcium oxalate stones through direct crystallization.

PSDs can cause hyperkalemia (< 3.5 mEq/l), especially in the elderly, in patients with renal failure, diabetes or receiving

Table 2. Pharmacokinetic parameters of loop diuretics and potassium-sparing diuretics.

	Bioavailability (%)	Onset (h)	Peak (h)	PPB (%)	Vd (l/kg)	Half-life (h)	Duration (h)	Renal excretion (%)	Dose (mg)
<i>Loop diuretics</i>									
Bumetanide*	50 – 90	0.5	1 – 2 (30 – 45 min i.v.)	97	0.15 – 0.28	1 – 1.5	4 – 6	36 – 69	0.5 – 4
Ethacrynic acid	> 90	30 min (oral) 5 min (i.v.)	2	99		0.5 – 1	6 – 8	65	25 – 200
Furosemide	10 – 90 (40)	0.3 – 0.5 10 min (i.v.)	1 – 2	99	0.07 – 0.35	1.3 – 3.5	6 – 8	49 – 94	20 – 240
Piretanide	80	0.5	1	85	0.25	1 – 2.5	6	52	2 – 12
Torsemide	80 – 92	0.3 – 0.5	1 – 2 (15 – 30 min i.v.)	99	0.09 – 0.3	3 – 6	12 – 16	22 – 34	5 – 20
<i>Potassium-sparing diuretics</i>									
Spirolactone	80 – 90	24 – 48 h	48 – 72 h	> 90	10	1.4 (13 – 24 h its metabolites)	3 – 5 days	< 1	25 – 100
Eplerenone	70	24 h	1.5	50	0.6 – 1.3	4 – 6	72 h	5	25 – 50†
Amiloride	15 – 25	2	4 – 6	-	5 – 7	6 – 9	24	50	5 – 20 (1)
Triamterene	50	2 – 4	6 – 8	60 – 70	2.2 – 3.7	1.8 – 2.5	12 – 16	20	25 – 100 (1)

*Bumetanide is not approved for hypertension.

†25 mg od when plasma K⁺ level > 5.5 mmol/l or creatinine plasma levels > 2.5 mg/dl; at higher levels, eplerenone is contraindicated.

F: Oral bioavailability; H: Hours; i.v.: Intravenous; PPB: Plasma protein binding in the urine; Vd: Volume of distribution.

K⁺ supplements, when coadministered with drugs producing hyperkalemia or in situations that predispose to hyperkalemia [39,74]. Reversible hyperkalemic metabolic acidosis has been reported in some patients with decompensated hepatic cirrhosis, even in the presence of normal renal function. To reduce the risk of hyperkalemia, patients should restrict dietary K⁺, reduce or avoid K⁺ supplements or salt substitutes containing K⁺ without consulting the prescribing physician. Dilutional hyponatremia may be caused or aggravated when spironolactone is coadministered with other diuretics.

Spirolactone can induce renal failure. The risk increases when it is coadministered with thiazide-like or loop diuretics; thus, this combination is recommended only if diuretic-related volume loss does not reduce the GFR. Because the package insert does not specify the level of CKD at which spironolactone is contraindicated, plasma creatinine and K⁺ levels should be regularly monitored in elderly and in patients with renal and hepatic impairment, particularly at initiation and on change of dosage. Eplerenone, however, is contraindicated in patients with a GFR ≤ 30 ml/min.

Spirolactone and triamterene should be avoided in pregnant women due to risk of feminization of fetus observed in animal studies and during lactation (Pregnancy Category C). However, there are no adequate and well-controlled studies with eplerenone in pregnant women (Pregnancy Category B). Amiloride is a folic acid antagonist and should be avoided during pregnancy.

3.5 Interactions

PSDs exert an additive effect when combined with other antihypertensives or vasodilatory drugs, tricyclic antidepressants or neuroleptics, while glucocorticoids and NSAIDs reduce their antihypertensive effects [3,35]. Additionally, NSAIDs increase the risk of acute renal failure. Coadministration with drugs that also raise serum K⁺ (ACEIs, ARBs, β-blockers, heparin i.v., trimethoprim-sulfamethoxazole, NSAIDs, pentamidine, drospirenone, heparin, tolvaptan, cyclosporin, tacrolimus, i.v. penicillin G potassium) and K⁺ supplements can precipitate serious hyperkalemia, particularly in older individuals or in patients with CKD [3,35,39].

Spirolactone presents a limited number of drug interactions. It decreases renal excretion of digoxin and increases serum digoxin levels and digitalis toxicity. Eplerenone plasma levels increase when combined with potent (clarithromycin, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, troleandomycin) and moderate CYP3A4 inhibitors (erythromycin, fluconazol, verapamil) [35,40]. Spirolactone and eplerenone increase the plasma Li⁺ levels, so that their levels should be monitored to avoid the risk of toxicity. The combination of indomethacin and triamterene can precipitate acute renal failure.

3.6 Contraindications and cautions

PSDs are contraindicated in patients with anuria, renal impairment (GFR < 30 ml/min/1.73 m², CKD Stages

4 – 5), hyperkalemia (> 5 mEq/l) or receiving K⁺ supplements or drugs that produce hyperkalemia or with additional risk factors for hyperkalemia [3]. Eplerenone is contraindicated: i) in patients treated with potent CYP3A4 inhibitors or inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, cyclosporin, tacrolimus, St John's Wort); ii) for the treatment of hypertension in patients with type 2 diabetes with microalbuminuria, serum creatinine > 2.0 mg/dl in males or > 1.8 mg/dl in females or creatinine clearance < 50 ml/min. In hypertensives receiving moderate CYP3A4 inhibitors, the starting dose of eplerenone should be reduced to 25 mg once daily.

4. New aldosterone antagonists

Despite their renal and cardiac benefits, MRAs (spironolactone and eplerenone) present several drawbacks limiting their clinical use. i) Spironolactone lacks MR selectivity and produces adverse effects related to its progestogenic and anti-androgenic activities, while eplerenone has lower affinity for MR and is less efficient than spironolactone to reduce BP in patients with mild-to-moderate hypertension [51]. ii) MRAs increase plasma renin and angiotensin II levels, and both plasma and tissular aldosterone levels remain elevated in patients long-term treated with MRAs, which may limit their long-term protective effect [37]. iii) Aldosterone produces rapid (occurring within minutes) non-genomic effects that are insensitive to MRAs [75].

These disadvantages stimulated the development of new nonsteroidal, highly potent, and selective MRAs. A number of dihydropyridine calcium channel blockers (CCBs) compete for aldosterone binding to the MR ligand-binding domain, block aldosterone-induced recruitment of co-activators and inhibit aldosterone-induced gene expression [76]. Furthermore, the MR S810L mutant, which is partially activated by spironolactone and eplerenone, is inhibited by these CCBs, which suggests that, unlike the steroidal MRAs, they function as full antagonists on this mutant receptor. BR-4628 is a dihydropyridine-based MRA, which displays high MR potency and selectivity with respect to other steroid hormone receptors and blocks L-type Ca²⁺ channels. BR-4628 accommodates in the MR ligand-binding cavity differently in comparison with the classical steroidal MRAs and forms complexes with the MR that do not promote the recruitment of transcriptional co-regulators [77]. These findings raise the possibility to develop a new generation of nonsteroidal MRAs with double actions, on L-type Ca²⁺ channels and MR.

Finerenone (BAY 94-8862) is a potent, selective nonsteroidal MR antagonist with high oral bioavailability (95% in rats) and long half-life (8.5 h) [78]. In experimental models of hypertension (spontaneously hypertensive stroke-prone and DOCA-salt rats), finerenone decreases vascular, cardiac glomerular and tubulo-interstitial hypertrophy and fibrosis and expression of several renal profibrotic genes without lowering BP [79,80]. In both models, finerenone produces more

pronounced cardiorenal end-organ protection than spironolactone and/or eplerenone. In patients with HF and reduced ejection fraction and mild or moderate CKD, finerenone (5 – 10 mg/day) is as effective as spironolactone (25 or 50 mg/day) to decrease biomarkers of hemodynamic stress and the plasma levels of brain natriuretic peptide (BNP), amino-terminal proBNP, and albuminuria as much as spironolactone, but produces less hyperkalemia and worsening of renal function [81]. Interestingly, the reduction in SBP and the rise in serum aldosterone levels in patients receiving finerenone are smaller than observed in patients receiving spironolactone, which could be an additional benefit in HF patients. PF-03882845 is another nonsteroidal aldosterone antagonist that is currently under clinical investigation (NCT00971802, NCT00856258).

Another approach to reduce aldosterone levels and inhibit its effects mediated via MR-dependent and MR-independent pathways is to inhibit the aldosterone synthase (CYP11B2) [82]. LCI699 is an orally active non-selective aldosterone synthase inhibitor as it also inhibits 11- β -hydroxylase (CYP11B1), the enzyme responsible for the final step in cortisol biosynthesis. In patients with primary aldosteronism, characterized by a high-aldosterone and low-renin status, sustained hypertension and hypokalemia, LCI699 decreases plasma aldosterone levels, corrects the hypokalemia and mildly decreases BP [83]. In hypertensive patients, LCI699 (1 mg od) is not superior in lowering BP to eplerenone 50 mg b.i.d. [84]. However, LCI699 blunts ACTH-stimulated release of cortisol in \approx 20% of subjects, due to its inhibitory effect on CYP11B1 [83,84]. Safety and tolerability are similar between LCI699 and placebo. These results support the development of new, more selective, aldosterone synthase inhibitors to avoid the inhibition of cortisol synthesis.

5. Diuretic drug combinations

When thiazide diuretics are not the first antihypertensive drug and the goal BP is not achieved, the addition of a thiazide (or loop diuretic) diuretic exerts an additive BP lowering effect because the diuretic exerts a different, but complementary, effect on peripheral vascular resistances, and can counteract the increase in Na⁺ and water retention produced by the other antihypertensives [8]. The increased renal tubular Na⁺ re-absorption increases extracellular fluid volume and blunts their antihypertensive effect.

There are numerous fixed combinations of HCTZ (6.25 – 25 mg/day) with β -blockers and RAAS inhibitors. Thiazides improve the antihypertensive efficacy of β -blockers in blacks and in patients with low-renin hypertension, while β -blockers attenuate the RAAS activation induced by thiazide diuretics, and the combination results in fully additive BP reduction [85]. However, this combination increases the risk of new-onset diabetes, fatigue, lethargy and sexual dysfunction. Carvedilol and nebivolol seem to be the exception.

The combination of a diuretic and a CCB results in a partially additive BP reduction presumably because CCBs also increase renal Na^+ excretion. Although this combination results in more vasodilation, it does not reduce the side-effect profile of each drug.

The preferred combination is a low-dose thiazide with an inhibitor of the RAAS (ACEI, ARB, MRA or aliskiren) because it leads to a fully additive BP reduction and allows the use of lower diuretic doses. Thiazides and loop diuretics induce a depletion of intravascular volume and activate the RAAS, which causes Na^+ and water retention and vasoconstriction, and RAAS inhibitors attenuate these counter-regulatory responses. Moreover, RAAS inhibitors decrease the metabolic adverse effects of the diuretics (hypokalemia and glucose intolerance), while thiazide diuretics minimize racial differences usually observed in response to monotherapy with RAAS inhibitors [1,5,86]. Thus, if low doses of thiazide diuretics (i.e., HCTZ 12.5 – 25 mg/day) are insufficient to reduce BP rather than increasing the dose, an ACEI or an ARAII, should be added to obtain a synergistic reduction in BP and counteract the diuretic-induced neurohumoral activation and metabolic disorders [87,88]. There are fixed-dose combinations of RAAS inhibitors (ACEIs or ARBs) with HCTZ and chlorthalidone (with azilsartan). Another effective and safe combination is a low-dose indapamide SR with low-dose perindopril [89]. Loop diuretics in combination with β -blockers, ACEIs (or ARBs) and MRAs (spironolactone or eplerenone) are of choice in patients with HF in the presence of signs and symptoms of fluid retention [64].

A thiazide (usually metolazone) can be used in combination with loop diuretics in patients with resistant edema, but with caution to avoid dehydration, hypovolemia, hyponatremia or hypokalemia. During the chronic administration of loop diuretics, the distal tubule is exposed to a high- Na^+ load leading to distal tubular cell hypertrophy and excessive re-absorption of Na^+ delivered from more proximal locations, so that the overall diuresis decreases [1,2]. Thiazide diuretics inhibit distal tubular hypertrophy and their combination with loop diuretics result in substantial natriuresis [1,2,15,17].

PSDs (spironolactone, eplerenone, amiloride, triamterene) are useful when coadministered with thiazides (HCTZ) and loop diuretics (furosemide) working at more proximal nephron locations. This *sequential nephron blockade* reduces the risk of hypokalemia and hypomagnesemia, provides additive natriuretic and antihypertensive effects in patients with diuretic resistance and reduces the risk of cardiac arrhythmias and sudden death in hypertensive patients [39,49]. PSDs are preferred to K^+ supplements as they correct both hypokalemia and hypomagnesemia. In fact, even at low doses (25 mg/day), spironolactone increases plasma Mg^{2+} and reduces the risk of ventricular and atrial premature beats and atrial fibrillation/flutter [39]. The spironolactone-HCTZ combination improves BP lowering and is particularly interesting in obese patients [84], while the combination of HCTZ with amiloride reduces hypokalemia but results in variable BP reduction [60].

These combinations are recommended in patients with an estimated GFR $> 50 \text{ ml/min/1.73 m}^2$; at lower GFR levels, the risk for hyperkalemia increases and the diuretic efficacy of thiazide diuretics decreases.

6. Expert opinion

The potency of loop diuretics to facilitate the excretion of sodium, and in particular, of water is the principal reason to consider their use in HF, CKD and cirrhosis. In some of these situations, like CKD, the association with a thiazide has demonstrated to be of value to further promote natriuresis and to increase urine volume. A similar additive diuretic effect can be obtained when combined to aldosterone blockers albeit this situation is limited by the level of renal function. The higher potency of this group of drugs can promote side effects similar to those of thiazide and thiazide-like diuretics but of higher intensity in some cases. Their use in the treatment of arterial hypertension is in general limited to the presence of CKD due to the short time of action that does not impede an inadequate renal sodium handling during a great part of the day when the drug is not active or to consider repeated doses with an increased risk of side effects. Aldosterone blockers are the drugs of choice in primary aldosteronism. These drugs are also considered when secondary aldosteronism is present in particular if it is promoted by loop diuretics. They were initially used in the treatment of arterial hypertension with apparently good results partly counteracted by the frequent side effects. In recent times, spironolactone, and in particular, eplerenone have been shown to be drugs of choice in HF with depressed LV ejection fraction and ongoing studies will show whether they are also positive in HF with preserved ejection fraction. Initial data indicate that these drugs are also very positive to diminish albuminuria when administered in combination with an ACEi or an ARB. This positive effect cannot be considered when eGFR is below $45 \text{ ml/min/1.73 m}^2$ due to the high risk of hyperkalemia, particularly in diabetic patients. Finally, a still-pending study in high-risk hypertensives is the comparison of an aldosterone blocker versus placebo to investigate the capacity of these drugs that are able to prevent CV events or death in those patients.

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Declaration of interest

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

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