The Forgotten Antiproteinuric Properties of Diuretics

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Keywords

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Abstract

Background: Although diuretics are one of the most widely used drugs by nephrologists, their antiproteinuric properties are not generally taken into consideration. **Summary:** Thiazide diuretics have been shown to reduce proteinuria by >35% in several prospective controlled studies, and these values are markedly increased when combined with a low-salt diet. Thiazide-like diuretics (indapamide and chlorthalidone) have shown similar effectiveness. The antiproteinuric effect of mineralocorticoid receptor antagonists (spironolactone, eplerenone, and finerenone) has been clearly established through prospective and controlled studies, and treatment with finerenone reduces the risk of chronic kidney disease progression in type-2 diabetic patients. The efficacy of other diuretics such as amiloride, triamterene, acetazolamide, or loop diuretics has been less explored, but different investigations suggest that they might share the same antiproteinuric properties of other diuretics that should be evaluated through controlled studies. Although the inclusion of sodium-glucose cotransporter-2 inhibitors (SGLT2i) among diuretics is a controversial issue, their renoprotective and

cardioprotective properties, confirmed in various landmark trials, constitute a true revolution in the treatment of patients with kidney disease. Recent subanalyses of these trials have shown that the early antiproteinuric effect induced by SGLT2i predicts long-term preservation of kidney function. **Key Message:** Whether the early reduction in proteinuria induced by diuretics other than finerenone and SGLT2i, as summarized in this review, also translates into long-term renoprotection requires further prospective and observational studies. In any case, it is important for the clinician to be aware of the antiproteinuric properties of drugs so often used in daily clinical practice.

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Introduction

Chronic kidney disease (CKD) is associated with increased morbidity and mortality, especially at later stages, which results in significantly higher health expenditures [1–3]. However, despite the high burden of CKD, only few therapies have proven to be effective for slowing or

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halting the progression. To a large extent, this is due to the slowly progressive nature of many forms of kidney diseases that challenge the design of clinical trials with hard end points [4]. Therefore, the use of surrogate end points to predict clinically relevant events and to investigate the potential effectiveness of new therapeutic strategies has become compulsory [5].

A large body of evidence has shown that albuminuria is among the most important markers to predict the risk of disease progression and the cardiovascular complications that frequently accompany CKD [6–8]. A sustained exposure and uptake of high amounts of albumin by tubular cells exert cytotoxic effects and trigger inflammatory pathways that ultimately lead to tubulointerstitial damage [4, 9–12].

Blood pressure control and albuminuria reduction represent the cornerstone of therapy to slow CKD progression. Renin-angiotensin system (RAS) blockers – either angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) – are a mainstay of therapy for both purposes [11–16]. Several pivotal trials have demonstrated the efficacy of these agents on the progression of both diabetic and nondiabetic nephropathies, mainly related to their antialbuminuric properties [12, 14–18]. However, a substantial proportion of patients are resistant to the antiproteinuric effects of these drugs and residual albuminuria may persist in others, despite maximum tolerated doses of RAS blockade, which in the long-term translates into progression of kidney damage [5, 19, 20].

Within the armamentarium of drugs that nephrologists use in their daily clinical practice, diuretics are among the most important drugs. Their antihypertensive effects have been demonstrated for a long time, and management of the edema caused by different proteinuric glomerular diseases or the volume overload that commonly accompanies CKD, particularly in its later stages, usually requires the use of diuretics. However, despite this familiarity of nephrologists with diuretic therapy, few clinicians take into consideration the antiproteinuric properties that various types of diuretics have shown in studies performed in the last years. Although the number of such studies is relatively small and their design has been focused mainly on the short term, most of them have obtained concordant results, showing a numerically important proteinuria reduction. The only diuretics whose antiproteinuric and renoprotective effects have been tested in large clinical trials with hard end points have been aldosterone antagonists (spironolactone, eplerenone, and finerenone). However, other types of diuretics widely

used in clinical practice, such as hydrochlorothiazide (HCT), chlorthalidone, indapamide, amiloride, or acetazolamide (AAZ) have also shown a remarkable antiproteinuric effect, at least in the short term. Noteworthy, most (if not all) studies that have proven that various diuretics decrease proteinuria have been designed on subjects who were already taking RAS blockers or on a low-salt diet. Thus, diuretics should be contemplated as a combination therapy for kidney protection. Given the increasingly established relationship between reduction in albuminuria and long-term renoprotection, the possible preventive effect these diuretics may have on the progression of CKD is a matter of utmost importance that should be explored by means of larger, prospective, and well-designed trials. In this review, we aimed to update the current knowledge and scientific studies addressing the antiproteinuric properties of diverse diuretics.

Thiazide Diuretics

Different clinical trials have shown that thiazide diuretics – alone or in combination with β -blockers, RAS blockade, and calcium antagonists – reduce morbidity and mortality in hypertensive individuals through a reduction in the incidence of congestive heart failure (HF) and stroke [21, 22]. The mechanism of action of thiazide diuretics is primarily mediated through inhibition of the sodium chloride cotransporter in the distal convoluted tubule, although other less prominent effects have also been described along the proximal and the cortical collecting tubule [23, 24]. Nonetheless, the natriuretic effect of thiazide diuretics is smaller than that of loop diuretics, which in general makes them less appropriate for edematous states. High-salt diet may elicit a change on renal hemodynamics toward hyperfiltration, especially in sodium-sensitive patients and those with a high body mass index [25–27]. This may be due to an inappropriate activity of the RAS [25].

Low-sodium diet enhances the antiproteinuric effects of RAS blockade [28, 29]. Indeed, the renoprotective and cardioprotective effects of RAS have been demonstrated to be greater during a concomitant low-sodium diet [30, 31]. However, in clinical settings and particularly with certain patients, this may be a difficult goal to achieve. The addition of low dose HCT has been shown to restore the antiproteinuric and blood pressure-lowering efficacy of RAS blockade, blunted by a high-salt diet [32]. Several studies have extensively analyzed the effect of sodium restriction and diuretic treatment on proteinuria reduction

in both nondiabetic and diabetic patients [33–38], and the most relevant evidence is summarized in the following lines:

Vogt et al. [35] examined in detail the separate and combined effects of a low-sodium diet and HCT on proteinuria and blood pressure in 34 nondiabetic patients. The authors found that both sodium restriction (1.2 g Na⁺ per day) and diuretic therapy (25-mg HCT) were equally effective in reducing proteinuria and blood pressure when added to RAS blockade (55 and 56%, respectively), although the largest effect on proteinuria was obtained during their combination (proteinuria reduction of 70% from baseline) [35]. Interestingly, sodium restriction and HCT led to similar decrease in kidney function during treatment with RAS blockade, and this decrease did not account for the decrease in proteinuria, suggesting that further reduction in proteinuria may be obtained by further sodium reduction [35].

Kwakernaak et al. [37] evaluated the independent and added effects of sodium restriction and HCT (in combination with RAS blockade) on residual albuminuria in a crossover randomized trial that included 45 patients with diabetes mellitus. Patients were given 50 mg HCT or placebo during 4 treatment periods of 6 weeks, and the latter were combined with sodium restriction (1.2 g Na⁺ per day) or a regular sodium diet. Both sodium restriction and HCT significantly reduced albuminuria irrespective of the sequence (44 vs. 39% albuminuria reduction from baseline), albeit this reduction was greatest when combined (57% albuminuria decrease) [37]. However, this combination was associated with a slight and reversible reduction in kidney function (Tables 1–4).

Another randomized trial assessed the potential benefit of HCT (12.5 mg/day) on proteinuria reduction among 102 patients with CKD under treatment with losartan (50 mg/day) [38]. After 12 months of treatment, a significantly greater degree of urinary protein-to-creatinine ratio reduction was observed in the group of patients who received HCT (mean urinary protein-to-creatinine ratio decline –0.55 g/g), without a significant difference in blood pressure, suggesting that the potential underlying mechanism could be independent of blood pressure reduction [38]. Similar results were reported in another small study that examined the renoprotective effects of thiazides combined with loop diuretics in patients with diabetic nephropathy, an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², and severe edema [39].

The exact underlying antiproteinuric mechanism of thiazides has not yet been elucidated, although it has been

suggested that they may induce a reduction in intraglomerular pressure through depletion of intravascular volume [35, 40, 41]. As a result, both body weight and total body volume decrease, and serum creatinine and uric acid may increase [40, 41]. The reported improvement in eGFR after discontinuing thiazide treatment and during the long-term follow-up is consistent with this proposed mechanism [42]. Thus, diuretics may induce immediate acute kidney function impairment, especially when combined with RAS blockade, but in the long-term, this could predict better kidney outcomes, possibly as a result of an improvement of glomerular hypertension [37, 42].

To summarize, all the aforementioned studies support the use of thiazides, especially for those patients who are unable to comply with a low-sodium diet, or as an add-on therapy in cases with significant residual albuminuria, despite maximum tolerated doses of RAS blockade, or a tendency towards hyperkalemia [32, 37, 40]. Nonetheless, this decision should be individualized according to the patient profile, considering the metabolic side effects of these agents [43], and also other potential long-term effects of thiazide exposure [44].

Thiazide-Like Diuretics

The antiproteinuric effects of thiazide-like diuretics – such as chlorthalidone and indapamide – have also been studied. A 12-week pilot study tested the effects of chlorthalidone in 12 patients with moderate to advanced CKD and found a 40–45% albuminuria reduction [41]. However, patients experienced a concomitant rise in serum creatinine at week 8 attributed to volume depletion, followed by a gradual improvement and return to baseline at 12 weeks [41]. This transient rise in serum creatinine was paralleled by a decrease in total body weight and an increase in renin and aldosterone levels [41].

Similar results have been reported in the kidney transplant population with an observed 30% proteinuria reduction and decrease of peripheral edema, albeit with a transient worsening in kidney function, which could otherwise complicate the assessment of a possible rejection [42]. Indapamide has also been shown to reduce albuminuria alone or in combination with RAS blockade in diabetic patients with persistent albuminuria [45–48].

Table 1. Summary of the main studies that evaluated the antiproteinuric properties of thiazide-type and thiazide-like diuretics

Authors	Type	Patients, <i>n</i>	Main outcome	Concomitant use of RAS blockade	Effect on proteinuria
<i>Thiazide-type diuretics</i>					
Buter et al. [32]	Prospective and crossover trial	7	Reduction of proteinuria	Yes (unspecified)	Addition of HCT reduced proteinuria by 37%
Vogt et al. [35]	Prospective, randomized, placebo-controlled, and crossover study	34	24-h proteinuria at the end of each treatment period	Losartan 100 mg/day	Combination of low-salt diet and HCT reduced proteinuria by 70%
Kwakernaak et al. [37]	Double-blind, placebo-controlled, and crossover, randomized trial	45	Reduction of albuminuria	Lisinopril 40 mg/day	Sodium restriction and HCT reduced albuminuria, especially when combined (56% reduction)
Fujisaki et al. [38]	Multicenter, open-label, and randomized controlled trial	102	Decrease in UPCR	Losartan 50 mg/day	Decrease in UPCR greater in patients with losartan-HCT than in the group of losartan alone
Morales et al. [40]	Prospective, randomized, and crossover trial	21	Decrease in uACR	Enalapril 40 mg/day	Reduction of uACR was greater with HCT with/without amiloride than with spironolactone (−56 vs. −42 vs. −34%)
<i>Thiazide-like diuretics</i>					
Gambardella et al. [47]	Prospective	21	Effect of indapamide on eGFR, albuminuria, and IgG4	No	66% albuminuria reduction after 24 months in patients with microalbuminuria
Molyneux et al. [46]	Randomized, open-label, crossover study	31	Effect of indapamide versus captopril in blood pressure, albuminuria, lipid profile, and HbA1c	No (comparison)	33% albuminuria reduction with indapamide versus 45% reduction with captopril
Marre et al. [45]	Multicentric, controlled, double-blind, randomized, and 2-parallel group study over 1 year	570	Effect of indapamide sustained release and enalapril in reducing albuminuria	No (comparison)	Mean reduction of 35% with indapamide versus 39% with enalapril
Agarwal et al. [41]	Single-center prospective trial	14	Change in systolic blood pressure in chlorthalidone group; change in albuminuria	Lisinopril 20–40 mg/day	Albuminuria was reduced by 40–45%
Moes et al. [42]	Randomized noninferiority crossover trial	49	Average daytime systolic blood pressure with amlodipine versus chlorthalidone; reduction of proteinuria	No	Similar blood pressure responses, but chlorthalidone reduced proteinuria by 30%
eGFR, estimated glomerular filtration rate; HCT, hydrochlorothiazide; RAS, renin-angiotensin system; UPCR, urinary protein-to-creatinine ratio; uACR, urinary albumin-to-creatinine ratio.					

Table 2. Summary of the main studies that evaluated the antiproteinuric properties of aldosterone antagonists

MRAS					
Authors	Type	Patients, <i>n</i>	Main outcome	Concomitant use of RAS blockade	Effect on proteinuria
Rossing et al. [57]	Randomized, double-masked, and crossover study	21	Determination of albuminuria, 24-h ambulatory BP, and GFR	Maximally recommended doses of losartan, irbesartan, enalapril,trandolapril, and ramipril	Albuminuria was reduced by 33% (95% CI, 25–41) after the addition of spironolactone
Schjoedt et al. [58]	Double-masked, randomized crossover trial	20	Evaluate the short-term effect of aldosterone antagonism on albuminuria and BP	Recommended doses of enalapril, ramipril, lisinopril, captopril, and losartan	Spironolactone on top of usual antihypertensive treatment induced a 30% (95% CI, 17–41) reduction in albuminuria
Chrysostomou et al. [56]	Single-center, double-blind, placebo-controlled, randomized intervention trial	41	Is angiotensin receptor blockade or aldosterone receptor antagonism more effective in combination with ACE inhibition? Does a higher level of blockade of the RAS with triple therapy offer an advantage over dual blockade?	Different doses of ramipril and irbesartan	Greater reduction (42–48%) in protein excretion at 3 months occurred in treatment regimens that incorporated spironolactone
Bianchi et al. [55]	Prospective randomized open-label study	83	Effects of spironolactone on proteinuria and eGFR in patients with CKD already treated with ACEIs and/or ARBs	Yes (unspecified)	Proteinuria decreased from 2.1±0.08 to 0.89±0.06 g/g creatinine (<i>p</i> < 0.001) in patients treated with spironolactone
Morales et al. [66]	Single-center prospective cohort study	87	Change of the mean eGFR from the first month of spironolactone treatment to the end of the follow-up	Yes (unspecified)	Spironolactone was associated with a 63% (range 44–77%) reduction in proteinuria versus baseline value
Boesby et al. [72]	Open randomized crossover trial	40	Evaluate the short-term antiproteinuric effect and safety of eplerenone	Yes (unspecified) – all patients but 2 were on RAS blockade	Mean urinary albumin excretion was 14% [CI, 4–24] lower during treatment
Bakris et al. [59]	Randomized, double-blind, placebo-controlled, and parallel group study	823	Ratio of the uACR at day 90 versus at baseline	Yes (unspecified) – at baseline, approximately 45% of patients were receiving ACEIs and 63% ARBs	Mean ratio of uACR at day 90 relative to baseline was reduced in all finerenone groups (for 7.5 mg/d, 0.79 [90% CI, 0.68–0.91]; for 10 mg/d, 0.76 [90% CI, 0.65–0.88]; for 15 mg/d, 0.67 [90% CI, 0.58–0.77]; for 20 mg/d, 0.62 [90% CI, 0.54–0.72])
Bakris et al. [60]	Randomized, double-blind, placebo-controlled, and multicenter clinical trial	5,674	Composite outcome of kidney failure, a sustained decrease of at least 40% in eGFR from baseline, or death from kidney causes	Yes (unspecified) – 98.1 and 98.8% of the patients were treated with ACEIs or ARBs, respectively	Finerenone was associated with a 31% greater reduction in albuminuria from baseline to month 4 (maintained thereafter)

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAS, renin-angiotensin system; uACR, urinary albumin-to-creatinine ratio; MRA, mineralocorticoid receptor antagonist.

Loop Diuretics

Loop diuretics are widely used in clinical practice for the treatment of systemic edema. However, only few studies have analyzed the potential antiproteinuric properties of loop diuretics when combined with standard RAS blockade. Esnault et al. [49, 50] found that a cautious increase in furosemide dosage in addition to combined half doses of ACEIs and ARBs better-decreased proteinuria than up-titration to the full dose of ACEIs and ARBs. This antiproteinuric effect could be partially explained by the concomitant eGFR decline due to volume depletion, suggesting the contribution of hemodynamic modifications in this effect [49, 50]. Nonetheless, it should be noted that increased furosemide dosage had also a profound effect over systolic blood pressure, advocating the possibility that the influence on proteinuria may have been a consequence of the hypotensive effect. Conversely, an experimental study failed to show added benefits of the combination of losartan plus furosemide – as compared to losartan plus HCT – in terms of blood pressure control, reduction of albuminuria and mortality in a 5/6 nephrectomy rat model [51].

Thus, it is not yet clear whether the antiproteinuric effect is achieved when an effective decrease in extracellular volume is achieved, leading to transient kidney function impairment. One must consider that there is no sharp evidence that thiazide or loop diuretics *per se* are capable of lowering proteinuria, rather, its mechanism of action in this context is probably related to the potentiation of the effect of RAS blockade by making intraglomerular pressure more RAS-dependent. The latter also applies to the effect of low-salt diet.

Aldosterone Antagonists

The physiologic functions of aldosterone on kidney sodium reabsorption, potassium handling, extracellular volume, and blood pressure homeostasis, are widely acknowledged. However, aldosterone also represents a major player for the development of vascular injury resulting in kidney fibrosis, and several animal models have shown that blocking aldosterone mitigates vascular damage and reduces proteinuria [52–54]. The myriad of beneficial effects of aldosterone blockade on kidney outcomes has been further established in humans in numerous randomized controlled trials [55–60].

Although one would expect that angiotensin blockade would ultimately suppress aldosterone, it has been observed that a subset of patients exhibits aldosterone es-

Table 3. Summary of the main studies that evaluated the antiproteinuric properties of loop diuretics, amiloride, and AAZ

Authors	Type	Patients, <i>n</i>	Main outcome	Concomitant use of RAS blockade	Effect on proteinuria
<i>Loop diuretics</i> Esnault et al. [50]	Multicentric, prospective, open-label, and randomized crossover study	18	Mean UPCR at the end of 3 treatment periods: ramipril 5 mg/day + valsartan 80 mg/day; ramipril 10 mg/day + valsartan 160 mg/day; ramipril 5 mg/day + valsartan 80 mg/day + increased furosemide	Yes (ramipril, valsartan at different doses)	Geometric mean UPCR was lower with combined therapy (ramipril + valsartan + furosemide)
<i>Amiloride</i> Unruh et al. [89]	Pilot double-blind randomized crossover study	9	Change in systolic blood pressure with amiloride or HCT in patients with type-2 diabetes mellitus and macroscopic proteinuria	No	15% uACR reduction in both arms
<i>AAZ</i> Zingerman et al. [94]	Randomized double-blind crossover study	12	Decrease in GFR following the administration of AAZ or furosemide at equipotent doses to obese nondiabetic patients	No	GFR decreased by 21% following AAZ, but did not decrease after furosemide, suggesting that AAZ could reduce hyperfiltration by activating TGF

AAZ, acetazolamide; GFR, glomerular filtration rate; HCT, hydrochlorothiazide; RAS, renin-angiotensin system; UPCR, urinary protein-to-creatinine ratio; uACR, urinary albumin-to-creatinine ratio; TGF, tubuloglomerular feedback.

Table 4. Main randomized controlled trials of SGLT2 inhibitors on kidney outcomes and albuminuria reduction

Trial characteristics	EMPA-REG outcome [108], (n = 7,020)	EMPEROR-reduced [109], (n = 3,730)	DAPA-CKD [110], (n = 4,304)	DECLARE-TIMI 58 [114], (n = 17,160)	CANVAS program [111], (n = 10,142)	CREDENCE [112], (n = 4,401)
Type of SGLT2i	Empagliflozin	Empagliflozin	Dapagliflozin	Dapagliflozin	Canagliflozin	Canagliflozin
Population	DM2, high CV risk	DM2/nondiabetics, high CV risk	DM2/nondiabetics, high CV risk	DM2, high CV risk	DM2, high CV risk	DM2, high CV risk
Concomitant use of RAS blockade	Yes – 80.7% were taking ACEIs or ARBs	Yes – approximately 70% without neprilysin inhibitor and 20% with neprilysin inhibitor	Yes – approximately 30% were taking ACEIs and 65% ARBs	Yes – 81.3% were taking ACEIs or ARBs	Yes – approximately 80% were taking ACEIs or ARBs	Yes – all patients
eGFR inclusion criteria	≥30 mL/min/1.73 m ²	≥20 mL/min/1.73 m ²	≥25 to ≤75 mL/min/1.73 m ²	≥30 mL/min/1.73 m ²	≥30 mL/min/1.73 m ²	≥30 to ≤90 mL/min/1.73 m ²
uACR inclusion criteria	–	–	200–5,000 mg/g	–	–	>300 to ≤5,000 mg/g
Kidney outcomes	Incident or worsening nephropathy (progression to macroalbuminuria, doubling of SCr, initiation of KRT, and death from kidney disease); incident albuminuria	Composite of chronic dialysis or KT or a profound, sustained reduction in eGFR	Composite of sustained decline in eGFR ≥50%, ESKD, death from kidney, or CV causes	Composite of ≥40% decrease in eGFR to <60 mL/min/1.73 m ² , new ESKD, death from kidney, or CV causes	Progression of albuminuria Composite of sustained 40% reduction in eGFR, need for KRT, or death from kidney causes	Composite of ESKD (dialysis, KT, or a sustained eGFR <15 mL/min/1.73 m ²), doubling of SCr, death from kidney, or CV causes
Follow-up (median)	3.1 years	16 months	2.4 years	4.2 years	126 weeks	2.6 years
Results	Kidney outcome occurred in 12.7% with empagliflozin versus 18.8% with placebo (HR 0.61; 95% CI 0.53–0.70) Doubling of SCr occurred in 1.5% with empagliflozin versus 2.6% with placebo (RRR 44%) KRT initiated in 0.3% with empagliflozin versus 0.6% with placebo (RRR 55%)	Kidney outcome occurred in 1.6% with empagliflozin versus 3.1% with placebo (HR 0.50; 95% CI 0.32–0.77)	Kidney outcome occurred in 9.2% with dapagliflozin versus 14.5% with placebo (HR 0.61; 95% CI 0.51–0.72)	Kidney events occurred in 4.3% with dapagliflozin versus 5.6% with placebo (HR 0.76; 95% CI 0.67–0.87) Death from any cause occurred in 6.2% with dapagliflozin versus 6.6% with placebo (HR 0.93; 95% CI 0.82–1.04)	Possible benefit on canagliflozin with respect to the composite kidney outcome (HR 0.60; 95% CI 0.47–0.77)	Primary outcome was 30% lower with canagliflozin (HR 0.70; 95% CI 0.59–0.82). ESKD, doubling of SCr, or death from kidney causes were lower by 34% with canagliflozin (HR 0.66; 95% CI 0.53–0.81) ESKD was lower by 32% with canagliflozin (HR 0.68; 95% CI 0.54–0.86)
Effect of SGLT2i over uACR	38% RRR for progression to macroalbuminuria No difference in rate of incident albuminuria	–	–	–	Possible benefit over progression of albuminuria (HR 0.73; 95% CI 0.67–0.79) Regression of albuminuria occurred more frequently (293 vs. 187 subjects with regression per 1,000 patient-years; HR 1.70; 95% CI 1.51–1.91)	Geometric mean of uACR was lower by 31% (on average)

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CI, confidence interval; CV, cardiovascular; DM2, diabetes mellitus type-2; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; KRT, kidney replacement therapy; KT, kidney transplantation; RRR, relative risk reduction; SCr, serum creatinine; uACR, urinary albumin-to-creatinine ratio; SGLT2i, sodium-glucose cotransporter-2 inhibitor; RAS, renin-angiotensin system; CKD, chronic kidney disease.

cape over time, with the resultant attenuation of the effect of ACEIs and ARBs treatment [61–63]. Thus, aldosterone blockade with mineralocorticoid receptor antagonists (MRAs) appears as a potential target for mitigating progression of CKD and might offer additive benefits to other antiproteinuric agents. In fact, the strongest evidence regarding the positive effect over proteinuria comes from studies where MRAs were introduced to patients who were already on ACEIs and/or ARBs treatment. Hence, when considering the use of MRAs with the aim of reducing proteinuria, these agents should ideally be used as an adjuvant therapy in subjects with maximized doses of ACEIs/ARBs [55, 56, 60]. Nonetheless, MRAs have a double effect: natriuresis and RAS inhibition. Therefore, decreased proteinuria may be achieved through the RAS-inhibitory effect, which in turn may be stimulated by the natriuretic effect, increasing RAS dependency. Considering this, MRAs might reduce proteinuria without concomitant RAS blockade and ultimately have an impact on kidney disease progression. Currently available MRAs include spironolactone, eplerenone, and finerenone.

Spironolactone

Spironolactone is a nonselective MRA that is metabolized in the liver to its active metabolite canrenone [64, 65]. In addition to the dreaded hyperkalemia, the structural similarity of spironolactone with progesterone accounts for the potential appearance of breast tenderness and gynecomastia [64]. Different studies have shown that the use of spironolactone on top of ACEIs and/or ARBs induces a proteinuria reduction of approximately 30–40% [55–57], and no additional benefit has been observed from triple blockade (ACEIs + ARBs + spironolactone) over dual blockade (ACEIs + spironolactone) [56]. Of note, albeit eGFR initially descends after spironolactone initiation, the monthly rate of eGFR decline is lower in treated patients in the long run [55, 58, 66]. In fact, MRAs in addition to ACEIs and/or ARBs are associated with a change in eGFR of $-2.38 \text{ mL/min/1.73 m}^2$ [65]. Interestingly, it has been observed that baseline aldosterone levels might predict the degree of reduction in proteinuria and the future rate of change in eGFR with MRAs therapy [55, 67]. On the other hand, the most recent evidence of MRAs over CKD progression comes from studies aimed at diabetic nephropathy. The renoprotective effects of spironolactone have been demonstrated in both type-2 and type-1 diabetic patients [56, 57, 67–70]. Of interest, it has been reported that albuminuria reduction is not necessarily correlated with the improvement in blood pressure control observed with aldosterone blockade, in both diabetic and nondiabetic patients [57, 71, 72].

Eplerenone and Finerenone

Eplerenone is a selective MRA that presents less affinity for progesterone receptors, and therefore lacks endocrinologic-related adverse effects [64], while finerenone is a novel selective nonsteroidal MRA that has demonstrated greater affinity than eplerenone and lower risk of hyperkalemia [59, 65]. In addition, finerenone has a distinct mechanism of action which translates into less pro-inflammatory and pro-fibrotic gene expression, with marked anti-fibrotic efficacy observed in preclinical models [73].

Until recently, the evidence on the reduction of proteinuria with eplerenone and finerenone was limited [67, 69, 71, 72, 74, 75]. In 2015, Bakris et al. [59] published the results of a large multicenter randomized controlled study that compared the antiproteinuric effect of finerenone versus matching placebo in subjects with type-2 diabetes mellitus with high or very high albuminuria who were already under ACEIs/ARBs treatment. Although the follow-up time was short, the finerenone arm presented a significant improvement in the urinary albumin-to-creatinine ratio (uACR) as compared to the control group [59]. Subsequently, the eagerly awaited results from the FIDELIO-DKD study have been recently brought to light [60]. In this large double-blind trial, the addition of finerenone to RAS blockade in type-2 diabetic patients resulted in lower risks of CKD progression and cardiovascular events than placebo after a median follow-up of 2.6 years. The primary composite outcome included kidney failure, a sustained decrease of at least 40% in eGFR from baseline, or death from kidney causes, which occurred in 17.8% of patients in the finerenone group versus 21.1% in the placebo group (hazard ratio 0.82; $p = 0.001$). Finerenone was associated with a 31% greater reduction in albuminuria from baseline to month 4, which was maintained thereafter. More patients on the finerenone arm exhibited hyperkalemia leading to drug discontinuation (2.3 and 0.9%, respectively). Of interest, despite multiple studies demonstrating positive results in patients with CKD, a recent Cochrane Database Systematic Review which included studies up to January 2020 reported that the effects of MRAs when added to ACEI or ARB (or both) on the risks of death, major cardiovascular events, and kidney failure in people with proteinuric CKD are still uncertain [76]. One must consider that the latter conclusions were based on evidence of very low to low certainty due to methodological limitations in the included studies and serious imprecision in estimated treatment effects. The majority of comprised studies enrolled a limited number of patients and were designed to observe dif-

ferences in surrogate end points (proteinuria and blood pressure) rather than patient-focused outcomes (kidney failure, death, and major cardiovascular events).

Additional Data on MRAs

Beyond its antiproteinuric and renoprotective effects, MRAs decrease morbidity and mortality in patients with HF and reduced ejection fraction. A recent systematic review found that these positive effects are also observed in CKD patients with HF and an eGFR between 30 and 60 mL/min/1.73 m². The authors reported that MRAs therapy reduces cardiovascular events, all-cause mortality, and HF hospitalization, despite higher risks of hyperkalemia and drug discontinuation in this subset of patients [77]. In contrast, a small randomized study found no effect of spironolactone on the cardiovascular parameters of maintenance hemodialysis patients [78]. On the other hand, MRAs have demonstrated to be effective for the management of resistant and refractory hypertension, and animal models have suggested a positive endovascular effect of finerenone through rebuilding vascular integrity and preventing development of vascular remodeling [79–82]. This is relevant since difficult-to-control hypertension and peripheral vascular disease are frequently encountered in the CKD population. Of interest, other novel nonsteroidal MRAs, such as apaliprone and esaxerenone are currently being tested in several clinical trials for other disorders, including nonalcoholic steatohepatitis and primary aldosteronism [83].

Amiloride and Triamterene

Amiloride and triamterene are other types of potassium-sparing diuretics that, unlike aldosterone antagonists, do not affect the mineralocorticoid receptor. Experimental studies have described an antiproteinuric effect of amiloride, attributed to the inhibition of urokinase-type plasminogen activator receptor expression in kidney podocytes [84, 85] (a molecule associated with cell motility highly expressed in podocytes and implicated in CKD progression) [86]. Additionally, it has been suggested that amiloride could further decrease proteinuria through an inhibition of the epithelial sodium channel on the distal nephron [87, 88]. One study reported the antiproteinuric effectiveness of amiloride as an adjuvant therapy in a patient with Fabry disease [87].

Unruh et al. [89] conducted a randomized double-blinded crossover study comparing the effects of the administration of amiloride or HCT to 9 diabetic patients

with proteinuria. Although no significant differences were observed in the primary outcome (change in systolic blood pressure) at the end of the study, the authors observed an almost 15% uACR reduction in both arms [89]. Finally, the preliminary results from an ongoing trial (NCT02522650), testing the effects of amiloride and triamterene on 12 proteinuric patients of different etiologies, reported a proteinuria reduction by 25% with the former and by 33.7% with the latter. Nevertheless, the risk of hyperkalemia remains the major concern associated with these drugs.

Acetazolamide

AAZ is a carbonic anhydrase inhibitor whose main indications are glaucoma and idiopathic intracranial hypertension [90]. The inhibition of carbonic anhydrase in the proximal tubule leads to bicarbonate, sodium, and chloride loss. In fact, it has been suggested that AAZ shares important similarities with sodium-glucose cotransporter-2 inhibitors (SGLT2i) as both act in the proximal tubule and suppress the sodium-hydrogen exchanger leading to natriuresis and a tendency towards metabolic acidosis (with normal anion gap in the case of AAZ and high anion gap with SGLT2i), which ultimately result in RAS inhibition and hyperfiltration reduction [91].

AAZ has long been used to prevent or attenuate acute mountain sickness [92]. Indeed, acute mountain sickness has been associated with the development of transient proteinuria, possibly due to renal hypoxia, which ultimately causes increased glomerular permeability, reduced tubular reabsorption, or both [93]. The treatment with AAZ has been shown to reduce proteinuria in this context [92, 93].

The effect of AAZ has also been evaluated on obesity-induced hyperfiltration. A randomized double-blinded crossover trial analyzed the effects of AAZ or furosemide at equipotent doses on glomerular hyperfiltration in 12 obese nondiabetic subjects [94]. GFR decreased by 21% following AAZ but did not decrease after furosemide, suggesting that AAZ could reduce hyperfiltration by activating tubuloglomerular feedback (TGF) [94].

Comparative Studies of the Antiproteinuric Effect of Different Diuretics

Our group was the first to perform a head-to-head comparison of the antialbuminuric effect of 3 different types of diuretics in a prospective randomized crossover study [40].

Twenty-one patients with CKD stages 1–3, baseline uACR >300 mg/g, and treatment with stable doses of RAS blockade during the last 3 months (before inclusion) were randomized to one of the following diuretic treatments: spironolactone 25 mg/day, HCT 50 mg/day, or HCT plus amiloride. Patients received each drug over a 4-week period, separated by washout periods of the same length. The results of this study revealed a significant albuminuria reduction with the 3 types of diuretics. Yet, the most novel finding was that patients treated with HCT achieved a median reduction of albuminuria of –42%. Moreover, when amiloride was combined with HCT, the reduction was much more pronounced, reaching a median of –56% from baseline (as compared to –34% albuminuria reduction with spironolactone alone). In addition, eGFR, blood pressure, and body weight decreased with the 3 therapeutic regimens, and a significant correlation was found between albuminuria reduction, eGFR, and blood pressure changes [40].

SGLT2is: Can They Be Considered as Diuretics?

The renoprotective mechanisms of SGLT2is, the new major players in diabetic nephropathy, seem to be more complex than initially thought. Inhibition of SGLT2 in the proximal convoluted tubule prevents glucose and sodium reabsorption. Likewise, SGLT2i also inhibits the sodium-proton exchanger, further increasing the delivery of sodium to the loop of Henle, which results in activation of TGF feedback response with consequent attenuation of glomerular hyperfiltration [95, 96]. Interestingly, preliminary studies pointed to a similar effect (reduction in intraglomerular capillary hydraulic pressure) with the use of AAZ [97]. Afar from the direct consequences over TGF and glycemic control, SGLT2i acts as osmotic diuretics, leading to a decrease in blood pressure and weight loss [98]. In a post hoc analysis of 2 randomized controlled trials, the use of dapagliflozin demonstrated osmotic and natriuretic diuretic effects in patients with type-2 diabetes and kidney involvement [99]. In addition, it was also observed that prolonged SGLT2i resulted in activation of compensatory mechanisms to reestablish extracellular volume homeostasis. Another remarkable observation is that the natriuretic effect of SGLT2i seems to be weaker than conventional diuretics since smaller increases in renin and aldosterone have been systematically reported [99–102]. As elegantly described by Eickhoff et al. [99], the latter observations suggest that osmotic diuresis seems to be the main factor involved in the diuretic effect of SGLT2i. It is important to consider that the diuretic and natriuret-

ic effects are restricted to subjects with an eGFR >45 mL/min per 1.73 m². On the other hand, SGLT2i has also been associated to reduction of oxidative stress and mitigation of kidney hypoxia [103–105]. The numerous mechanisms involved in the cardiorenal protection of SGLT2i have been recently described in detail elsewhere [106].

SGLT2is have demonstrated to reduce the risk of progression of kidney disease (worsening of kidney function, end-stage kidney disease, and kidney death) by 45%, regardless of cardiovascular disease status. The extent of benefit seems to be more pronounced in those with less severe kidney disease at baseline. On the contrary, the impact on cardiovascular outcomes appears to be greater in those with worse baseline eGFR [107]. As today, numerous randomized controlled trials and subanalysis involving different SGLT2is (empagliflozin, canagliflozin, and dapagliflozin) have systematically demonstrated a sharp renoprotective and cardioprotective effect, even in patients without diabetes and in those with advanced CKD [108–114]. Nonetheless, in spite of all the evidence favoring the use of SGLT2i in proteinuric kidney diseases (particularly in diabetic patients), the possible association between renoprotection and the antiproteinuric effect of these agents has not yet been elucidated. A recent study based on simulation analyses showed that even small albuminuria-lowering effects of dapagliflozin significantly reduced the estimated kidney risk [115]. Additionally, a post hoc analysis from the CRE-DENCE trial found that canagliflozin significantly increased the likelihood of achieving an albuminuria reduction at week 26, and each 30% decrease in uACR was independently associated with a lower risk for the primary kidney outcome and major adverse cardiovascular events [116]. On the contrary, the DIAMOND trial found that a 6-week treatment with dapagliflozin did not affect proteinuria but did induce an acute and reversible decline in measured GFR and a reduction in body weight, suggesting that clinical kidney outcomes may be driven by nonproteinuric pathways [117]. Of note, although SGLT2i may potentiate the effect of concomitant RAS blockade, these agents are capable of lowering albuminuria irrespective of the presence of RAS blockers. Hence, these drugs can be given along with the aim of reducing proteinuria.

Changes in Albuminuria as a Surrogate End Point for Progression of Kidney Disease

Several studies and meta-analysis published in recent years suggest that a treatment-induced reduction in albuminuria, regardless of the type of therapeutic interven-

tion, translates into a long-term renoprotective effect [7, 8, 118–120]. In fact, a meta-analysis that included almost 30,000 patients strongly support that lowering albuminuria represents a surrogate end point for the progression of CKD, especially in subjects with high baseline albuminuria [7]. Conversely, worsening proteinuria has never been associated to an improved outcome [121]. Nonetheless, other investigations propose that it is still uncertain whether aiming at proteinuria reduces risk of patient-focused outcomes such as kidney failure and death of any cause [76].

Since early preclinical studies, it has been observed that increased glomerular filtration of proteins accelerates the progressive loss of nephrons that ensues in CKD [11]. Experimental models have shown that accumulation of filtered proteins in proximal tubular cells causes basement membrane disruption, followed by an inflammatory reaction, development of interstitial damage, and glomerular sclerosis [11, 122]. Molecules that attract macrophages and T cells, such as monocyte chemoattractant protein-1 and RANTES, were overexpressed in proximal tubular cells that were challenged with plasma proteins [121, 123, 124]. Also, proteinuria enhanced endothelin-1 production, activation of transcriptional NF- κ B, and upregulation of pro-fibrogenic factors, such as TGF- β [124–127]. On the other hand, protein overload has been suggested as a potential direct stimulus for the upregulation of the complement factor C3 at the proximal tubule [128]. Therefore, based on the latter observations, proteinuria appears as a paramount agent in the pathophysiology of the progression of proteinuric kidney diseases. However, it is still unanswered which proteins play a predominant role as activators of tubular cells.

Albuminuria has been on the spotlight for many years, but in recent times, its importance has been highlighted by the results of the latest clinical trials based on SGLT2i and finerenone therapy. It is worth noting that reduction of uACR has been observed early after treatment onset and that the short-term reduction in albuminuria observed with SGLT2i has been associated with a decreased risk of long-term cardiovascular and kidney outcomes [116, 129].

This concept, also investigated in IgA nephropathy [120], has implications of enormous importance for clinical practice, since an early and strong antialbuminuric response to a particular therapeutic measure, as well as its maintenance over time, might be crucial to ensure long-term renoprotection. On the contrary, increased doses or combinations of antialbuminuric drugs ought to be con-

sidered in those patients with a poor antialbuminuric response. The design of clinical trials to investigate the possible renoprotective efficacy of a drug would change drastically if the decrease in albuminuria is accepted as a surrogate end point for end-stage kidney disease [130, 131]. Considering the characteristic slow progression of most proteinuric kidney diseases, such a conceptual change would boost the performance of trials with a simpler, cheaper, and faster design. Obviously, such a decisive change needs an in-depth discussion by the nephrology community and further analysis. Moreover, determining the percentage of albuminuria reduction that ensures effective long-term renoprotection, as well as the albuminuria thresholds above which such renoprotective effect is weakened, or whether these thresholds are different depending on the type of kidney disease, requires further studies.

Conclusions and Future Research

In the present work, we have summarized the mechanisms of action and beneficial effects of diverse diuretics over proteinuria, and we have conducted an in-depth update of the most recent research in the field. Classic diuretics have been used for a long time in the clinical setting; however, the antiproteinuric effect of these agents remains largely unknown, even by the nephrology community. Landmark studies have unequivocally demonstrated the renoprotective effect of finerenone and different SGLT2is in addition to the standard of care (RAS blockade), and recent subanalyses of these studies showed that the early antialbuminuric effect induced by these drugs predicts long-term preservation of kidney function. Whether the premise that a reduction in albuminuria is a valid surrogate marker for long-term renoprotection can be transferred to other diuretics (spironolactone, eplerenone, thiazides and thiazide-like diuretics, amiloride, indapamide, and AAZ) whose antiproteinuric properties have been summarized in this review requires more prospective and observational studies. It is essential to keep in mind that studies that have evaluated the antiproteinuric effect of different diuretics have been performed under circumstances of RAS blockade or low-salt diet; therefore, diuretics should be considered as very important agents in combination therapy. Also, it cannot be excluded that the effect on proteinuria represents a consequence of the influence of diuretics over blood pressure, although the direct effect of lowering blood pressure as a renoprotective mechanism is still controversial. In

any case, considering the crucial value of the amount of albuminuria for the progression of proteinuric nephropathies, it is important for the clinician to be aware of the antiproteinuric properties of drugs so frequently used in daily clinical practice.

Conflict of Interest Statement

There are no conflicts of interest to declare.

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Author Contributions

Conception: M.P.; library search and identification of articles: H.T., F.C.F., J.C., E.M., and M.P.; summarization of articles: H.T., F.C.F., and M.P.; manuscript writing and drafting: H.T., F.C.F., and M.P.; the final approval of the manuscript: all authors.

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