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Application of Direct Renin Inhibition to Chronic Kidney Disease

Christian W. Mende

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Abstract
Purpose Chronic kidney disease has serious implications with a high risk for progressive loss of renal function, increased cardiovascular events as well as a substantial financial burden. The renin-angiotensin-aldosterone system (RAAS) is activated in chronic kidney disease, especially in diabetes and hypertension, which are the leading causes of chronic kidney disease. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) decrease the rate of progression of diabetic and non-diabetic nephropathy and are recommended therapy for chronic kidney disease.
Methods Key clinical trials supporting the use of ACE inhibitors and ARBs in chronic kidney disease are discussed. Recent developments in our understanding of RAAS biology and the use of direct renin inhibition are reviewed in the context of their potential impact on the prevention and management of chronic kidney disease.
Results Despite the clinical success of ACE inhibitors and ARBs the rates of mortality and progression to renal failure remain high in these patient populations. ACE inhibitor or ARB monotherapy, in doses commonly used in clinical practice does not result in complete suppression of the RAAS. Aliskiren, a direct renin inhibitor, offers a novel approach to inhibit the RAAS in chronic kidney disease.
Conclusions High dose ARB therapy or combination therapies with ACE inhibitors and ARBs have shown beneficial effects on surrogate markers of chronic kidney disease. Early data based on urinary protein excretion rates as a surrogate marker for renal function suggest a possibly novel role for aliskiren alone or in combination with ARBs in chronic kidney disease.

Key words Aliskiren · Renin · Angiotensin · Kidney disease

C. W. Mende (✉)
Department of Medicine, University of California at San Diego,
6950 Fairway Road,
La Jolla, CA 92037, USA
e-mail: cmende4730@aol.com

Introduction

Chronic kidney disease is defined as kidney damage, as assessed by biopsy or markers of kidney damage, for ≥3 months with or without changes in glomerular filtration rate, or a glomerular filtration rate ≤60 ml/min/1.73 m^2 for ≥3 months with or without kidney damage [1]. Chronic kidney disease is an increasingly prevalent problem that is debilitating, increases premature morbidity and mortality, and is very costly to manage. The prevalence of chronic kidney disease in the United States in 1999–2004 was estimated to be between 13.1% [2] and 16.8% [3] and will likely continue to increase given the prevalence of obesity, diabetes and hypertension, all risk factors for chronic kidney disease [3].

Chronic kidney disease is a frequent prelude to end stage renal disease. Patients with end stage disease must receive renal replacement therapy consisting of either renal transplant or dialysis. Despite these therapies, the 5 year survival rate for patients with end stage renal disease year is only 38% [4]. End stage renal disease occurs in 0.03% of the US population, but the management of this disease consumes nearly 7% of the Medicare budget [5]. As of 2007, Medicare and non-Medicare costs for end stage renal disease had reached $20.1 billion and $12.4 billion, respectively. The most recent estimate suggests annual Medicare costs of $68,000, $49,000, and $24,000 for hemodialysis, peritoneal dialysis, and transplant patients, respectively [5].

The cost of managing chronic kidney disease varies depending on comorbidities, but it is far less expensive than managing end stage renal disease. In an analysis of over 30 million members across 35 health plans with records from 2000 to 2006, 11,531 patients with diabetes, 74,759 patients with hypertension, and 4,779 patients with both conditions were identified [6]. The adjusted annualized incremental all-cause health care costs associated with chronic kidney disease were $7,190 in the diabetes cohort, $5,450 in the hypertension cohort, and $9,177 in the diabetes+hypertension cohort. So, if chronic kidney disease costs at least $5,000 per year in all 46 million US patients, that would translate into $230 billion of incremental all-cause health care costs—if all these patients were members of these health insurance plans.

Chronic kidney disease is associated with an increased risk of cardiovascular events, death and hospitalizations, and these risks increase proportionally to kidney functional decline [7]. The importance of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of chronic kidney disease is widely appreciated, and this understanding is due largely to the results obtained with pharmacologic agents that block the system. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) slow the progression of chronic kidney disease[8–10] and are recommended as first line therapy in the treatment of this disease [11].

Over the past few years our understanding of the complexity and pervasive effects of the RAAS has grown as new components, functions and regulatory steps have been identified. Moreover, a new drug class, direct renin inhibitors, has been developed that offers another therapeutic option to suppress the RAAS in cardiorenal diseases. The focus of this review is to discuss recent developments in RAAS biology of potential clinical relevance to chronic kidney disease and the potential impact of direct renin inhibition on the prevention and management of chronic kidney disease.

Overview of the renin-angiotensin-aldosterone system and new developments

The RAAS is a coordinated cascade of sequential enzymatic steps, the first of which is the release of renin from juxtaglomerular cells in the kidney. (Fig. 1) Renin is formed by the proteolytic removal of a 43 amino acid prosegment peptide from its precursor, prorenin [12]. Renin is stored in secretory granules and is released in response to decreases in renal perfusion pressure, decreases in Cl^- in the distal tubule fluid or increased sympathetic nerve stimulation via β1 adrenoceptors. Renin release can also be inhibited by a direct action of angiotensin II on the juxtaglomerular cells. Many other factors are known to modify renin release and/or expression including vitamin D [13], uric acid [14], TGFβ [15], and TNFα [16]. Renin acts on circulating angiotensinogen derived from the liver as well as locally produced to form angiotensin I (Ang I). Ang I is converted to the active peptide, angiotensin II (Ang II), by membrane bound ACE.

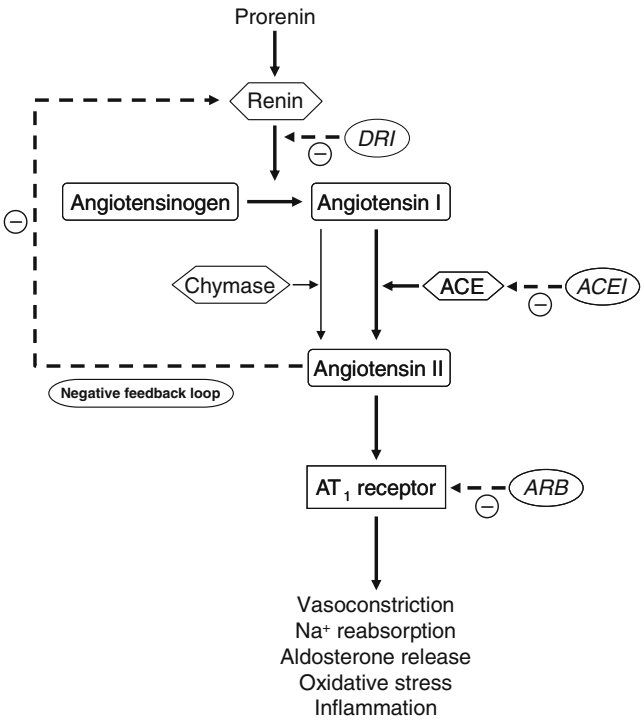

Fig. 1 The renin-angiotensin-aldosterone system. DRI, direct renin inhibitor; *ACE*, angiotensin converting enzyme; *ACEI*, angiotensin converting enzyme inhibitor; *ARB*, angiotensin receptor blocker

Other active and inactive metabolites can be formed from Ang I and II by ACE-2, a homologue of ACE. ACE-2 is expressed in the kidney, heart and other organs and is not inhibited by ACE inhibitors [17]. ACE-2 generates the biologically active peptide, Ang (1–7), from Ang II and the inactive peptide Ang (1–9) from Ang I [17, 18]. Ang (1–7) by activating its receptor, Mas, has actions that generally opposed those of Ang II including vasodilation and antiproliferative effects [17]. In mouse models of diabetic nephropathy ACE-2 is down regulated [19] and knockout of ACE-2 or inhibition of its activity promotes proteinuria and worsens glomerular injury in this model [19, 20]. Therefore, during RAAS activation ACE-2 may counter act the actions of ACE by forming Ang (1–7) and by breaking down Ang I [17, 18].

Intrarenal renin-angiotensin-aldosterone system

The circulating RAAS is an endocrine system that exerts primary control over the maintenance of extracellular fluid volume and (together with the autonomic nervous system) the regulation of blood pressure. In addition, many tissues, especially those associated with the cardiovascular system, contain all or some of the components of the RAAS and

can therefore form Ang II locally. These "local" or "tissue" based systems can function independently of the traditional circulating system and are thought to act in a paracrine manner to regulate organ function, growth and cellular proliferation, and are involved in pathological events associated with end organ damage [21]. The kidney contains all the elements of the RAAS, and intrarenal formation of Ang II independent of the circulating system has been amply demonstrated [22].

Angiotensin II

Ang II acts on at least 2 different receptor subtypes, the type 1 (AT_1) and type 2 (AT_2) receptors [12]. The AT_1 receptor is the predominate receptor in most tissues and mediates all of the classic physiologic and pathophysiologic actions of Ang II. In addition to the well known actions of Ang II to induce vascular smooth muscle contraction, activate Na^+ transport in the proximal tubule and to stimulate aldosterone release from the zona glomerulosa in the adrenal glands, Ang II has been implicated in the processes of inflammation and endothelial dysfunction, both of which are associated with hypertension and chronic kidney disease. For example, Ang II activates NAD(P)H oxidases and xanthine oxidase producing reactive oxygen species such as peroxynitrite, superoxide anion and hydrogen peroxide, which reduce nitric oxide bioavailability and contribute to endothelial dysfunction [23]. Ang II also activates the transcription factor, NF-kB, which induces the formation of chemokines and cell adhesion molecules that are involved in the inflammatory process [24]. In addition, Ang II appears to be an important mediator in the induction of TGFβ, tissue remodeling, fibrosis, and extracellular matrix formation, all of which are processes involved in the pathogenesis of diabetic nephropathy [24] (Fig. 2).

Aldosterone

In addition to its well known actions in promoting Na^+ reabsorption by the kidney, there is now clear evidence that aldosterone-mediated activation of the mineralocorticoid receptor in non-epithelial tissues of the heart, kidney, and vasculature induces fibrotic changes in these tissues [25], contributes to oxidative stress and vascular inflammation [26], and is associated with endothelial dysfunction [27].

Prorenin and the (pro)renin receptor

The discovery of the (pro)renin receptor [28] has added another dimension to the complexity of the RAAS. This receptor, which is present in many organs including the heart and kidney, binds both renin and prorenin [29]. Binding of renin to this receptor increases its catalytic activity. More importantly, prorenin, which is normally inactive, becomes catalytically active following binding to this receptor without undergoing proteolysis and thus can contribute to local Ang II formation [29]. This may be of particular importance in diseases such as diabetes in which prorenin is significantly elevated and represents 95% of circulating renin [30].

Activation of the (pro)renin receptor in mesangial cells also activates mitogen-activated protein kinase, ERK 1 and 2 and several fibrosis/remodeling mediators such as TGFβ and PAI-1 [28, 31]. These effects are independent of Ang II as they occur in the presence of ACE inhibitors or ARBs [28]. Although more research is needed, activation of the (pro)renin receptor may contribute to the pathology of renal disease by increasing local Ang II formation and by increasing the expression of profibrotic mediators. However, the in vivo effects of (pro)renin receptor overexpression on end organ damage in experimental animals are mixed and

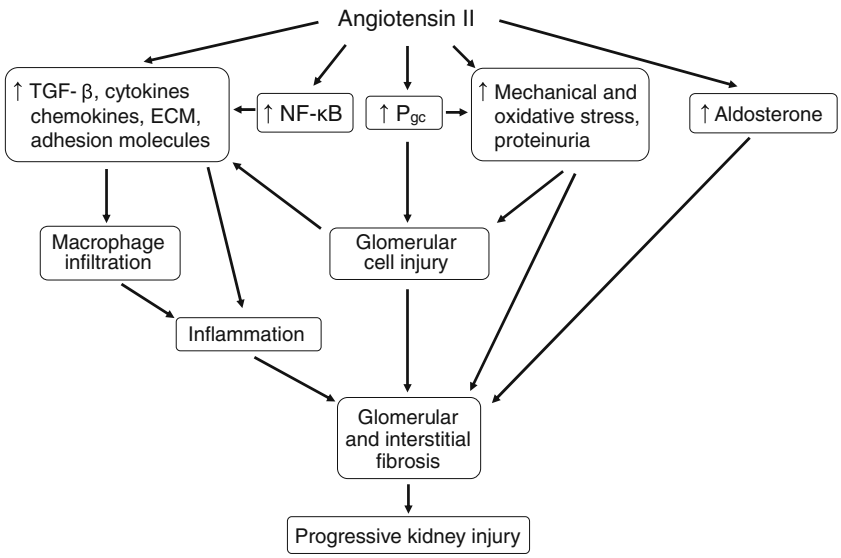

Fig. 2 Multiple roles of angiotensin II in the pathogenesis of chronic kidney disease. Pgc, glomerular capillary pressure

therefore the role of this receptor in chronic kidney disease remains to be determined [32].

Role of the renin-angiotensin-aldosterone system in chronic kidney disease

Chronic kidney disease is associated with increased cardiovascular events, premature mortality, decreased quality of life, and increased health-care expenditures [3]. Diabetes and hypertension are the leading causes of chronic kidney disease [11] and there is now ample experimental and clinical evidence showing that the intrarenal RAAS is activated and plays a critical role in the pathogenesis of chronic kidney disease [33–36].

Experimental studies

Early studies in experimental models of renal disease led to the proposal that following renal injury and decrements in glomerular filtration rate the remaining viable nephrons undergo structural and functional compensatory changes which increase glomerular filtration rate sufficiently to meet excretory demands [37]. Chief among these adaptations is an increase in glomerular capillary pressure. However, the increase in glomerular pressure results in injury to glomerular epithelial and endothelial cells and mesangial cell expansion. These changes ultimately lead to further glomerular damage and a vicious cycle of progressive nephron loss [37]. Ang II is one of the main regulators of glomerular pressure, and ACE inhibitors, but not other antihypertensive agents, were found to prevent the rise in glomerular pressure and to offer protection against proteinuria and glomerulosclerosis in these animal models [37].

Clinical trials with angiotensin converting enzyme inhibitors and angiotensin receptor blockers

Based largely on preclinical data in chronic kidney disease models a number of clinical trials were conducted to assess the effects of ACE inhibitors and subsequently, ARBs, on the progression of diabetic and nondiabetic nephropathy. The first such trial examined the effects of captopril in patients with type 1 diabetic nephropathy. After a median follow up of 3 years, patients receiving captopril as compared to placebo had a 48% reduction in the risk of doubling of serum creatinine and a 50% reduction in the combined risk of death, dialysis and transplantation [8]. In patients with chronic kidney disease of various etiologies, benazepril resulted in a 53% reduction in the doubling of serum creatinine or the need for dialysis [38].

Two subsequent studies evaluated the effects of ARBs in patients with nephropathy associated with type 2 diabetes. In the Irbesartan Diabetic Nephropathy Trial (IDNT)[9], the effect of irbesartan on renal and cardiovascular morbidity and mortality was compared to that of amlodipine and placebo. For subjects receiving irbesartan treatment, the relative risk of reaching the primary composite endpoint of doubling of serum creatinine, end-stage renal disease or death from any cause was 20% lower than the placebo group and 23% lower than the amlodipine group. Similarly, in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study (RENAAL) [10], losartan reduced the risk of doubling of serum creatinine, end stage renal disease or death by 16% compared to the placebo group. While losartan treatment was associated with a 28% reduction in the risk of end stage renal disease, there was no effect on the rate of death. In all these trials the benefits of renin-angiotensin-aldosterone system blockade on chronic kidney disease appeared to be beyond those attributable solely to changes in blood pressure. Based on these results, ACE inhibitors or ARBs are recommended as first line therapy for chronic kidney disease [11].

Optimizing renin-angiotensin-aldosterone system blockade

While it is clear that ACE inhibitors and ARBs reduce the progression of chronic kidney disease in some patients, these agents have not been shown to reduce mortality in this population, and the majority of patients continues to lose renal function and eventually do progress to end stage renal disease. There are a number of possible reasons for this. In early trials such as RENAAL and INDT the treatment regimens did not reduce blood pressure to today's aggressive goals of <130/80 mmHg and in RENAAL 37% of the patients had no proteinuria reduction at all. Furthermore, factors such as salt intake can have a major impact on the progression of chronic kidney disease especially in the early stages of the disease. Hypertension in chronic kidney disease is often salt sensitive and changes in salt intake in the physiologic range can have major effects on blood pressure and can also attenuate the therapeutic effectiveness of RAAS inhibition [39].

Polymorphism of the genes encoding for the various components of the RAAS may also affect the response to treatment in patients with chronic kidney disease. The best characterized of these is the insertion (I)/deletion (D) polymorphism of the *ACE* gene. Patients carrying the D allele (DD or DI) have a greater risk of developing diabetic nephropathy compared with the II genotype [40, 41]. ACE inhibitor therapy seems to be most effective in patients with type 1 or type 2 diabetes with the II genotype at earlier stages of chronic kidney disease [42]. In patients with type

2 diabetes and overt albuminuria, ARBs are more effective in reducing outcomes in patients with the DI or DD genotype compared to the II genotype [41]. Polymorphisms in the genes of other components of the RAAS have been described but their role in kidney disease progression or effects on treatment regimens are still under investigation [42].

Other potential reasons for suboptimal clinical outcomes with ACE inhibitors and ARBs may be associated with insufficient blockade of the RAAS with currently used dosing, especially in the setting of an activated intrarenal system as occurs in diabetes [43]. In up to 50% of patients chronically treated with ACE inhibitors, Ang II levels gradually returned to baseline [44]. This phenomenon has been termed "ACE escape" and is likely due to a compensatory increase in plasma renin activity due to disruption of the feedback loop by which Ang II normally inhibits renin release [12]. Under these circumstances Ang II can be formed from Ang I by alternative, ACE-independent pathways, such as chymase, which has been shown to be upregulated in diabetic and hypertension related nephropathies [45]. Likewise, ARBs increase plasma renin activity due to inhibition of the Ang II-renin release feedback loop [46]. In this case the increase in Ang II may compete with the ARB for the AT1 receptor [47]. Since renal outcomes appear to be directly related to the degree of blood pressure and proteinuria reduction [48, 49], optimizing RAAS blockade with ACE inhibitor/ARB combination therapy or high dose ARB has been explored mostly in small groups of patients using proteinuria as a surrogate maker.

Angiotensin converting enzyme inhibitor/angiotensin receptor blocker combination therapy

In patients with comorbid type 2 diabetes, microalbuminuria and hypertension, the combination of candesartan and lisinopril produced greater reductions in mean sitting diastolic and systolic blood pressures than did the respective monotherapy [50]. The change in the urinary albumin/creatinine ratio with combination therapy (−50%) was significantly better than that observed in the candesartan group (−24%) but was similar to that seen in the lisinopril group (−39%). The recent analysis of renal outcomes in the large ONTARGET trial [51] found that ramipril/telmisartan combination therapy decreased proteinuria but worsened the primary renal composite outcome of dialysis, doubling of serum creatinine and death when compared to ramipril and telmisartan monotherapy in patients at high vascular risk**.** This result was surprising in that proteinuria is a risk factor in patients with type 2 diabetic nephropathy and reductions in proteinuria lead to proportional increases in renal protection [52]. However, this trial was not powered to detect differences in major renal outcomes [51] and overt proteinuria was present in only 12.2% of patients with diabetes and in only 4% of all patients at study entry [51]. Moreover, proteinuria was measured only at 2 year intervals [51] versus the recommended 2 or 3 times a year [11]. Furthermore, in the combination therapy group, the rate of decline in estimated glomerular filtration rate was only slightly above that due to normal aging [53]. Therefore, while this trial suggests that telmisartan/ramipril combination therapy has no renal (or cardiovascular) benefit and may be harmful in patients with little or no proteinuria, this trial did not address the efficacy of ACE inhibitor/ARB combination therapy on renal outcomes in patients with chronic proteinuric kidney disease**.** Three trials are currently underway that target this issue. Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID, NCT00494715) and the VA NEPHRON-D Study (NCT00555217) [54], are evaluating the ability of ACE inhibitor/ARB combinations to decrease mortality and the progression to end stage renal disease in patients with diabetic nephropathy. The Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) trial is evaluating if combined treatment with ACE inhibitors and ARBs compared with monotherapy is associated with additional cardiorenal benefits, in subjects with microalbuminuria and 1 or more cardiovascular risk factors [55].

High dose angiotensin receptor blocker therapy

Small, short term studies have examined the effects of high dose ARB treatment on proteinuria in patients with diabetes and proteinuria. Doses of ARBs at 2 to 4 times the maximum recommended doses further reduced protein excretion in these patients with little or no additional effects on blood pressure [56–58]. These high doses of ARBs were generally well tolerated and, while serum potassium levels increased in some patients, rates of hyperkalemia (K^+ >5.5 mEq/l) were low. However, long-term renal outcome data are lacking for this potentially promising treatment regimen.

Aldosterone antagonism

In some patients, ACE inhibitors and ARBs suppress aldosterone levels only transiently and they slowly return to baseline levels over the course of weeks. Observational studies have shown that this phenomenon, known as "aldosterone breakthrough", occurs in up to 41% of patients with diabetic nephropathy treated with an ARB [59]. These findings, together with the observation that aldosterone blockade in combination with ACE inhibitors or ARBs reduces kidney damage in experimental models of renal disease, have led to a resurgence of interest in the use of aldosterone antagonists in the treatment of chronic kidney

disease [60]. Aldosterone receptor antagonists reduce proteinuria in patients with proteinuric kidney disease who are already receiving ACE inhibitors or ARBs [61]. Moreover, pilot studies suggest that adding aldosterone antagonists on a background therapy of angiotensin converting enzyme inhibitors or angiotensin receptor blockers may decrease the rate of loss of kidney function in chronic kidney disease patients [62]. Well-designed outcome studies are required to determine whether addition of aldosterone antagonists to angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy is safe, especially as it relates to potassium homeostasis, and translate into better outcomes in patients with chronic kidney disease.

Direct renin inhibition

Inhibition of renin activity has long been considered to be the logical step to interrupt the RAAS as it is the initial and rate limiting step in the formation of Ang I. Aliskiren, alone or combined with hydrochlorothiazide or valsartan, is the first FDA-approved, orally active direct renin inhibitor, a new class of compounds designed to inhibit the RAAS. Unlike ACE inhibitors, ARBs and other antihypertensive agents that cause an increase in plasma renin activity, aliskiren directly inhibits the catalytic activity of renin, thus reducing plasma renin activity and, in turn, the production of Ang II and aldosterone [63]. Moreover, aliskiren can counteract the increase in plasma renin activity induced by ACE inhibitors, ARBs, calcium channel blockers and diuretics [64–67] (Fig. 3). Therefore, direct renin inhibitors have the potential of more comprehensive suppression of the RAAS than ACE inhibitors and ARBs.

Results from several clinical studies support this contention. For example, studies in healthy volunteers [68, 69] and in patients[70] have shown that aliskiren decreases elements of the RAAS (Ang II, plasma renin activity and aldosterone) to a greater extent than ARBs. Moreover, in volunteers, maximum doses of aliskiren increased renal blood flow 2-fold greater than maximum doses of ACE inhibitors and 40% greater than ARBs [71]. In a number of trials aliskiren has been shown to produce marked reductions in aldosterone. For example, in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial aliskiren when combined with losartan reduced urinary aldosterone by 24% after 6 months compared with a 4% decrease with losartan alone [72]. Likewise, in the Aliskiren in Left Ventricular Hypertrophy (ALLAY) study plasma aldosterone was reduced by 21% from baseline with aliskiren/losartan combination therapy, compared with a 5% increase with losartan alone 9 months after the start of therapy [72]. Finally, in patients with symptomatic heart failure, aliskiren when combined with optimal therapy (ACE inhibitor or ARB and beta blocker) reduced urinary aldosterone by 19% compared with an increase of 2% with placebo [73]. Combined, these results suggest that aliskiren may provide more comprehensive suppression of the circulating and intrarenal RAAS than ACE inhibitors or ARBs [30].

Experimental studies have shown that aliskiren has the potential to reduce end organ damage in chronic kidney disease. For example, in animal models of hypertension and heart and kidney damage, aliskiren reduced mortality, proteinuria and end organ damage [74–77]. Importantly, another study showed that aliskiren extensively partitioned

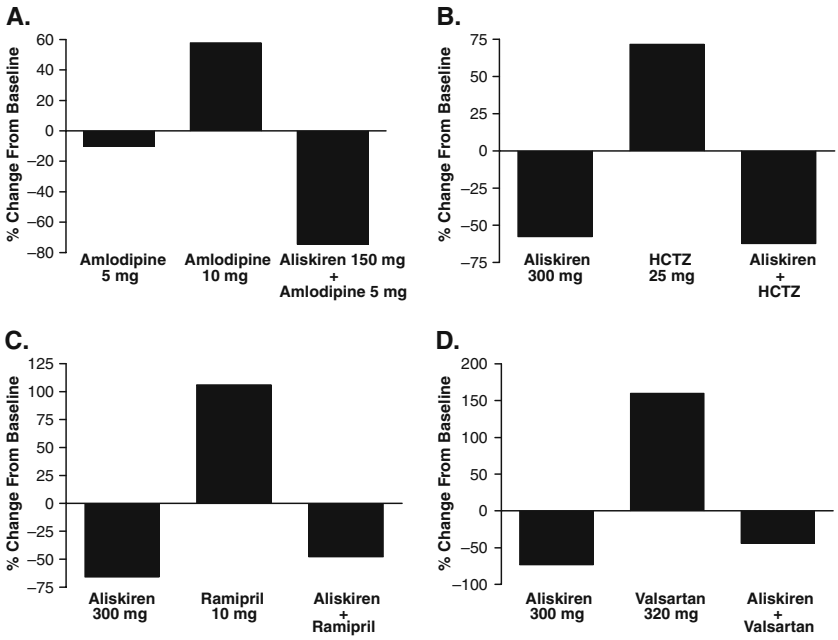

Fig. 3 Effect of aliskiren alone or in combination with amlodipine (**a**), hydrochlorothiazide (HCTZ) (**b**), ramipril (**c**) and valsartan (**d**) on plasma renin activity. Results represent the percentage change from baseline. Data are from Drummond et al., 2007 [64], Villamil et al. 2007 [65], Uresin et al., 2007 [66] and Oparil et al., 2007 [67]

to the kidney [76]. This fact may explain the marked and long lasting aliskiren-induced increases in renal blood flow observed in normal volunteers [71], as well as the persistent blood pressure-lowering effects of aliskiren in hypertensive patients following drug withdrawal [78–80].

The mechanisms of renoprotection observed in preclinical studies with aliskiren are still under investigation. However, in addition to inhibiting the formation of Ang I by the circulating and intrarenal RAAS [77], aliskiren has also been shown to reduce the renal expression of the (pro) renin receptor in an animal model of diabetes [76]. Thus, aliskiren may contribute to end organ protection by reducing the deleterious actions of Ang II and the Ang II-independent effects of (pro)renin receptor activation.

In clinical studies, aliskiren has been shown to be an effective and long-acting antihypertensive agent when used alone [79–81] or in combination with other antihypertensive drugs [64–67]. Thus far, 3 studies have evaluated it as a potential renoprotective agent in chronic kidney disease, using proteinuria as a surrogate marker. In a small exploratory study designed to investigate the time course of aliskiren treatment, patients with type 2 diabetes and micro- or macroalbuminuria recieved aliskiren and furosemide but no other RAAS blockers [78]. Mean 24 h systolic blood pressure but not diastolic blood pressure was reduced by 6 mmHg at treatment end (28 days). The urinary albumin creatinine ratio progressively decreased from baseline with treatment and a maximum reduction of 44% was obtained the end of the treatment period. Urinary albumin creatinine ratio remained below baseline for approximately 12 days following washout. Compared to baseline, plasma renin activity was reduced by 68% and Ang II by 42% at the end of treatment. After aliskiren withdrawal plasma renin activity and Ang II remained below baseline for 1 week and gradually returned to pretreatment levels by 4 weeks.

In a larger study, the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial [82], the effects of dual blockade of the RAAS with aliskiren plus losartan were evaluated in patients with comorbid hypertension and type 2 diabetes with nephropathy. Patients who were maintained on losartan (100 mg daily) for the duration of the study were randomized to receive aliskiren (150 mg/d for 3 mo, then 300 mg/d for 3 mo) or placebo. Three months of treatment with the combination of aliskiren/losartan (150/100 mg/d), reduced the urinary albumin creatinine ratio by 11% compared with losartan alone. Increasing the dose of aliskiren to 300 mg/d further decreased albumin excretion to 20% by the end of the study**.** Urinary aldosterone was reduced from baseline by 24% in the aliskiren/losartan group versus those patients receiving losartan alone (−4%) [72]. The reduction in proteinuria occurred in the absence of significant changes in blood pressure suggesting that addition of aliskiren to losartan had potential renoprotective effects independent of blood pressure. The rates of adverse events or discontinuations between the 2 groups were similar. Hyperkalemia was reported in 5.0% and 5.7% of patients in the aliskiren and placebo groups, respectively.

The potential renoprotective effects of aliskiren were further examined in an exploratory study of the antiproteinuric effects of 300 mg aliskiren compared to, and in combination with, 300 mg irbesartan, or placebo in a double blind, randomized cross-over trial [70]. Patients with type 2 diabetes, hypertension and albuminuria (>100 mg/day) underwent a 1-month washout period with no antihypertensive medications, but received furosemide to prevent blood pressure elevation. Following this, they were randomly assigned to receive each of the 4 treatments (aliskiren 300 mg, irbesartan 300 mg, placebo or combination aliskiren+irbesartan using identical doses) for 2 months. Aliskiren was as efficient as irbesartan in reducing the urinary albumin excretion rate: 48% and 58%, respectively ($P<0.001$ vs placebo for both treatments; P=ns between treatments) [70]. The urinary albumin excretion rate was reduced with the combination by 71% ($P<0.001$ vs placebo), which was significantly greater than that seen with aliskiren ($P<0.001$) or irbesartan ($P=0.028$) monotherapy. The added antiproteinuric effect with combination treatment compared with aliskiren alone was about 31%. This additional decrease in proteinuria with the combination therapy was directly and proportionately correlated with an increase in plasma renin concentration, supporting the concept of increased intrarenal RAAS suppression by aliskiren. The patients enrolled in this small study had a lower mean baseline UAER compared with that in the AVOID trial. In contrast to the AVOID study, which reported an additive antiproteinuric effect with aliskiren added to a maximal recommended dose of losartan and optimal antihypertensive therapy, this study directly compared the antiproteinuric effects of aliskiren monotherapy with ARB monotherapy in addition to confirming the additive effects seen with the combination [70].

These 3 studies demonstrate that aliskiren alone or combined with an ARB reduced albumin excretion in patients with diabetic nephropathy, suggesting that direct renin inhibition may be an additional treatment option in patients with type 2 diabetes and nephropathy. While these initial results are promising, larger long-term trials that measure cardiovascular and renal outcomes such as progression to end stage renal disease and cardiovascular mortality are needed to explore the potential beneficial effects of direct renin inhibition on chronic kidney disease. Such trials are ongoing, which will determine whether aliskiren in combination with an ACE inhibitor or an ARB reduces endpoints of cardiorenal morbidity and mortality in

high risk patients with type 2 diabetes (ALTITUDE) [83] or whether aliskiren added to standard therapy reduces mortality and hospitilizations in patients with heart failure (ATMOSPHERE, NCT00853658).

Safety and tolerability

In a pooled analysis of data from over 7000 patients with hypertension treated with aliskiren for 6 to 8 weeks, the overall incidence of adverse events (AEs, 39.8%) was similar to placebo (40.2%) [84]. More than 95% of the AEs were mild or moderate with headache, nasopharyngitis, diarrhea, and dizziness being the most commonly reported. The incidence of hyperkalemia (potassium >5.5 mmol/L) with aliskiren treatment (150 mg, 0.7%; 300 mg, 1.0%) was similar to placebo (0.6%) Combination of aliskiren (150 mg or 300 mg) with ramipril, amlodipine, valsartan or hydrochlorothiazide (HCTZ) resulted in an AE profile similar to that of the respective monotherapy. However, the rate of cough was lower with ramipril/aliskiren therapy (1.8%) compared with ramipril alone (4.7%). Likewise the rate of edema was lower with aliskiren/amlodipine therapy (2.1%) compared with amlodipine alone (11.2%) [84]. Rates of hyperkalemia were low and similar to the respective monotherapy when aliskiren was combined with amlodipine, valsartan, or HCTZ. However, hyperkalemia was higher in patients receiving aliskiren/ramipril (5.5%) compared with ramipril alone (2.6%). In a longer term (6 months) study of patients with hypertension receiving aliskiren/valsartan or aliskiren/valsartan/HCTZ, the most frequent AEs were headache, nasopharyngitis, diarrhea, and dizziness [85]. Hyperkalemia was reported in 2.0% of patients and was transient.

In the 2 short-term studies that evaluated the effects of aliskiren in patients with diabetic nephropathy, no hyperkalemia was observed [70, 78]. In the longer term AVOID trial [82] there was no difference in the overall incidence of AEs between patients recieving losartan alone (67.1%) versus the losartan/alsikiren group (66.8%). Likewise the rates of hyperkalemia (5.7% vs 5.0%) were similar between the groups. In the losartan/alsikiren group 14 patients (4.7%) experienced potassium levels ≥6.0 mmol/L versus 5 (1.7%) in the losartan group. However, 9 of the 14 patients treated with losartan/aliskiren had elevated baseline potassium and should have been excluded from the study. These studies suggest that the AEs associated with aliskiren alone or in combination with ARBs are generally mild and similar to current therapies. However, as with ACE inhibitors and ARBs, serum electrolyte levels including potassium need to be monitored in patients with impaired renal function when using aliskiren [86].

Summary and conclusions

Chronic kidney disease is a major healthcare problem that will likely continue to increase due to the ageing population and the elevated prevalence of hypertension, diabetes and obesity. The RAAS is activated in chronic kidney disease and pharmacological modulation of this system has become a cornerstone in the treatment of this disease. While ACE inhibitors and ARBs have been shown to retard the progression of chronic kidney disease, the majority of patients still progress to end stage disease or die from cardiovascular events. There is a vast need for further improvement in the therapy of patients with chronic kidney disease.

Current evidence suggests that inhibition of the RAAS with ACE inhibitors and ARBs stimulates a compensatory increase in plasma renin activity that may negate some of the beneficial effects of these agents. Therefore, strategies that more fully suppress the RAAS in chronic kidney disease are being explored. High dose ARB therapy or combination therapies with ACE inhibitors and ARBs have shown beneficial effects on surrogate markers of chronic kidney disease. Direct renin inhibition with aliskiren represents a novel and potentially more effective way to inhibit the RAAS. Unlike ACE inhibitors and ARBs, plasma renin activity is inhibited with aliskiren, and downstream components of the RAAS are suppressed. Like ACE inhibitors and ARBs, aliskiren, alone or in combination with an ARB, has been shown to reduce proteinuria in patients with diabetic nephropathy. However, whether these new treatment regimens confer better outcomes in patients with chronic kidney disease await the results from ongoing clinical trials with appropriate endpoints.

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Conflict of interest Dr. Christian W. Mende has received speaking honoraria from Novartis, Forest, Bristol Myer Squibb and Glaxo and has served on an advisory board of Novartis.

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