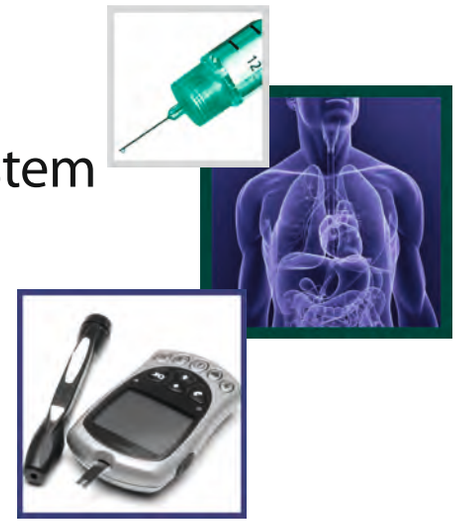
REVIEW

Blockade of the renin–angiotensin system for the primary prevention of diabetic nephropathy



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Practice Points

- The prevention of chronic kidney disease is a primary goal for diabetes management.
- Lowering blood pressure can reduce the incidence of microalbuminuria in Type 1 or Type 2 diabetes, especially in patients with hypertension.
- Blockade of the renin–angiotensin system (RAS) is an effective strategy to reduce blood pressure in diabetic patients, but no more so than other antihypertensive strategies.
- RAS blockers have a more favorable side-effects profile compared to other antihypertensive agents, meaning that generally patients are more likely to take them.
- Any 'independent' effect of RAS blockade for the primary prevention of diabetic nephropathy, beyond blood-pressure control, remains to be clearly established.
- New combination strategies using renin inhibitors or aldosterone antagonists, to achieve a more complete RAS blockade, have the potential to improve renal outcomes in patients with diabetes.

SUMMARY There is clear evidence for the pathogenic role of the renin–angiotensin system (RAS) in the progression of diabetic kidney. Treatment with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker have been shown to reduce proteinuria and preserve renal function in patients with diabetes and chronic kidney disease. While such data provide a strong rationale for early and sustained blockade of the RAS for the primary prevention of kidney disease, clinical trial evidence to support this goal is limited and inconsistent. By contrast, data from observational and clinical trials clearly demonstrate the primacy of blood-pressure control in the development of diabetic kidney disease, especially in hypertensive patients. Whether RAS blockade offers additional benefits for primary prevention, over-and-above blood-pressure control, remains contentious. At best, any 'independent effects' on primary prevention are modest, and certainly not the panacea envisaged by many practitioners. However, the better tolerability, efficacy and side-effects profile of RAS blockers, and other actions on retinopathy and cardiovascular disease, means that most patients with diabetes currently receive RAS blockers as first line antihypertensive agents. The future development of more effective 'escape-proof' regimens currently offers the best way forward to realize the hope that RAS blockade will ultimately prevent diabetic kidney disease in the clinic as effectively as it does in animal models.

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Treatment with either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) have been shown unequivocally to reduce proteinuria and preserve renal function in patients with diabetes and chronic kidney disease (CKD) [1–3]. Such findings have led to widespread recommendations for agents that block the renin–angiotensin system (RAS) to be considered as the first-line treatment for the management of diabetic CKD. However, even in patients receiving RAS blockers, the anticipated morbidity and mortality observed in those with CKD, far exceeds that observed in patients without CKD [4]. Consequently, interventions that reduce the incidence of CKD are fundamentally more important for the management of diabetes. It is currently anticipated that between 25 and 40% of patients with Type 1 diabetes develop diabetic kidney disease. Twenty to forty percent of patients with Type 2 diabetes also develop kidney disease [5,6], mostly within 10 years of diagnosis [7]. With this incidence and given that over 300 million individuals have diabetes worldwide [8], the prevention of diabetic kidney disease represents an overwhelming clinical priority.

There is clear evidence for the pathogenic role of the RAS in the development of diabetic kidney [9]. For example, genetic overactivity of the RAS is associated with increased incidence and severity of kidney disease in animal models of experimental diabetes [10,11]. The incidence of microalbuminuria is also increased in patients with diabetes who are homozygous for the D allele of the *ACE* gene [12]. Such data provide a strong rationale for early and sustained blockade of the RAS for the primary prevention of kidney disease in all patients with diabetes. However, clinical trial evidence to support this goal is limited and inconsistent. Furthermore, its interpretation has been made more difficult because RAS blockers also lower blood pressure (BP), a key pathogenic factor that in its own right, significantly contributes to the development of microalbuminuria in diabetic patients **(Figure 1)**. Indeed, it has been argued that the better, more sustained and less variable effects of RAS blockade on BP may partly explain the so-called 'independent' benefits with respect to the primary prevention of kidney disease. This review specifically explores the utility of RAS blockade for the primary prevention of incident microalbuminuria, and the opportunities for creating a more complete blockade, and with it, potentially a more effective renoprotection.

Blood-pressure control for the prevention of diabetic kidney disease

The control of BP represents a key target for the prevention of diabetic kidney disease [13,14], as well as other microvascular complications [15]. Although hypertension can be a result of renal dysfunction, in many cases, hypertension may precede the onset of CKD, suggesting that it is also a key etiological factor [16,17]. Renal damage in hypertensive animal models of diabetes is more pronounced than in normotensive models [18,19]. For example, studies in the diabetic spontaneously hypertensive rat show that BP reduction, regardless of its modality, is associated with significant renoprotection [20]. Yet surprisingly, studies examining the utility of BP lowering in patients with diabetes have revealed only variable effects for the primary prevention of CKD, possibly reflecting variability in the kind of patients recruited in these trials, and in particular, their comorbidities including hypertension.

In patients with Type 1 diabetes from the Microalbuminuria, Cardiovascular and Renal Outcomes-Heart Outcomes Prevention Evaluation (micro-HOPE) study, treatment with the ACE inhibitor, ramipril (10 mg/day) effectively lowered the BP and significantly reduced the incidence of microalbuminuria when compared with placebo [21]. However, among patients with Type 1 diabetes in the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes study who were normoalbuminuric at baseline, no significant reduction in the incidence of microalbuminuria were observed in patients using the ACE inhibitor, lisinopril (10–20 mg), despite a small but significant reduction in diastolic BP [22]. Similarly, in a *post-hoc* analysis of the Diabetic Retinopathy Candesartan Trial (DIRECT), the ARB, candesartan (16 mg/day), did not reduce new onset microalbuminuria in patients with Type 1 diabetes, although the rate of change of albuminuria was modestly lower [23].

When compared with studies in Type 1 diabetes, there is much better evidence that BP reduction reduces the incidence of microalbuminuria in patients with Type 2 diabetes [13,14]. There have been a number of primary-prevention studies in patients with Type 2 diabetes using a variety of antihypertensive agents including ACE inhibitors, ARBs, calcium channel blockers (CCBs), α-blockers, and β-blockers, usually given in combination [13,14]. For example, in the UKPDS study of patients with Type 2 diabetes,

a reduction of BP from 154 to 144 mmHg was associated with a 30% reduction in microalbuminuria [15]. In the large Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation treatment with the ACE inhibitor, perindopril and indapamide (4 and 1.25 mg daily) lowered the systolic BP by approximately 7 mmHg and reduced new-onset microalbuminuria by 26% when compared with conventional antihypertensive treatment [24]. There was no BP threshold below which renal benefit was lost. New-onset macroalbuminuria was also modestly reduced in the large Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial by aggressively targeting lower systolic BP levels (~120 mmHg), but incident microalbuminuria was not prevented **(Figure 2)** [25].

Each of these studies was conducted in heterogeneous populations, with a significant proportion of patients with established or incident hypertension of variable etiology. Consequently, in patients with Type 2 diabetes the use of blood-pressure lowering in the absence of an elevated BP remains controversial. In the UKPDS study, no threshold for the impact of elevated BP was able to be determined for any outcome [15]. This conclusion has also been inferred from meta-analysis data, which found that the efficacy of BP reduction appears to be independent to the baseline BP [14]. Indeed, it has been argued that there is no such thing as a normotensive diabetic [26]. However, studies that have tried to examine the utility of antihypertensive agents in normotensive subjects, comparing their renoprotective actions against placebo, have been largely disappointing. For example, in normotensive patients with Type 2 diabetes from the micro-HOPE study, the ACE inhibitor, ramipril (10 mg/day) did not reduce the incidence of new-onset microalbuminuria [21]. Similarly, in Type 2 diabetic patients enrolled in the DIRECT study the ARB, candesartan (16 mg/day) failed to reduce the development of microalbuminuria, despite lower BP levels in the candesartan-treated group [23].

Better blood-pressure lowering by blocking the RAS

There is no doubt that drugs that block the RAS are effective antihypertensive agents. When used as monotherapy, RAS blockers can achieve reduced BP levels similar to that achieved by other antihypertensive interventions. However, in some aspects of BP control, there are data to suggest that RAS blockers may be different to other blood-pressure lowering strategies, even for the same achieved reduction in mean BP levels observed at clinic visits. For example, some have argued that the benefits of RAS blockade observed in the (micro-HOPE) study may simply reflect the better 24 h and night time control of BP achieved with ramipril (10 mg/day) [27].

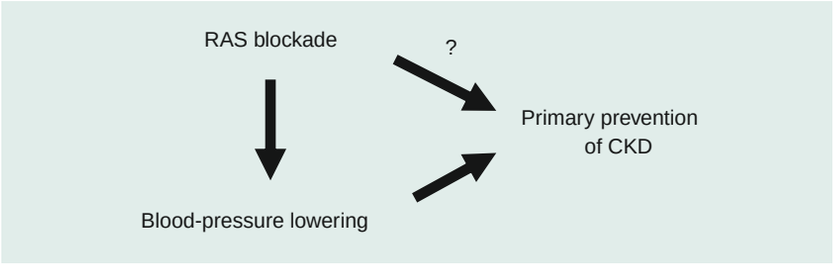

Figure 1. Blood-pressure dependent and independent actions of renin–angiotensin system blockade on the primary prevention of kidney disease in patients with diabetes.
CKD: Chronic kidney disease.

Another difference between BP lowering strategies may be their effects on BP variability, beyond similar lowering mean blood-pressure levels. For example, it is known that visit-to-visit variability in BP are independently associated with the risk of diabetic nephropathy, over and above mean BP control [28]. Indeed in the DCCT study, visit-to-visit variability in BP explained as much of the variability in incident nephropathy as differences in mean BP [28]. Despite lowering the BP, monotherapy with RAS blockers may paradoxically increase visit-to-visit variability when compared with other antihypertensive classes [29]. In theory this may offset renoprotective gains in other areas achieved through RAS blockade and potentially contribute to the inconsistent findings observed in clinical trials using monotherapy or few other agents. By contrast there is also some suggestion that antihypertensive combinations that contain RAS blockers result in the least BP variability [30]. Potentially this may explain why renoprotective advantages have been largely reported in studies of hypertensive patients when RAS blockade is one of usually three or four different antihypertensive agents.

The other key advantage of RAS blockade is its tolerability and compliance [31]. Although ACE inhibitors may induce a troublesome cough in some individuals, compliance with ACE inhibitors is better than with CCBs or diuretics,

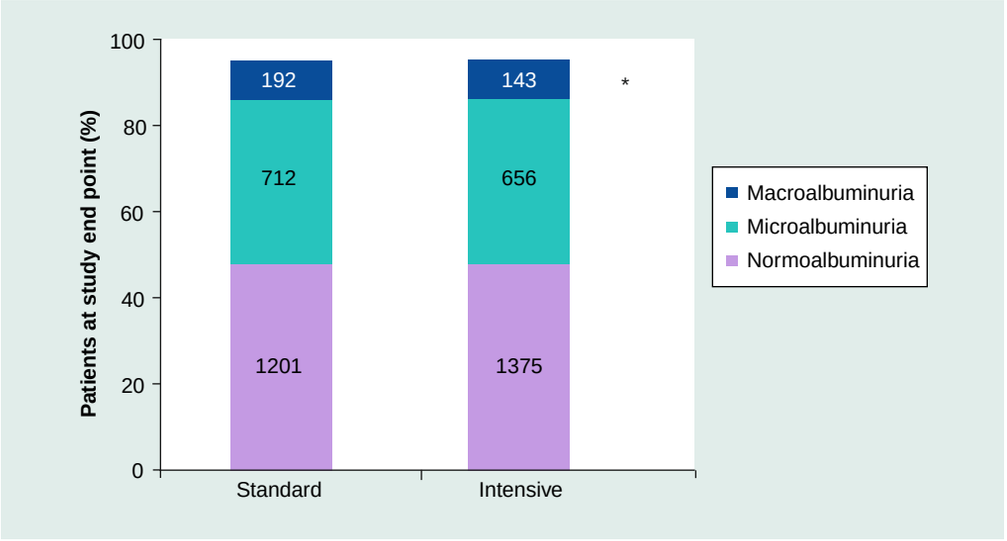

Figure 2. Urinary albumin excretion status at end point in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial comparing aggressively targeting lower systolic blood-pressure levels (<120 mmHg) to standard therapy (<140 mmHg).
*Versus standard therapy (p = 0.009).
Data taken from [25].

which are signficiantly limited by edema and urinary frequency, respectively. β-blockers have important cardioprotective actions in patients with diabetes, independent to blood-pressure lowering, but are also hampered by effects on lethargy, sleep disturbance and effects on glucose control. ARBs appear to be, on average, the most tolerated of all antihypertensive agents. Taken together, these effects mean that patients prescribed RAS blockers are generally more likely to be taking them [31], which ultimately translates into better BP control on an intention to treat basis.

Beyond blood-pressure lowering: a rationale for blocking the RAS

Activation of the intra-renal RAS and the subsequent generation of angiotensin II (Ang II) appear to be among the most important initiators of renal injury in diabetic kidney disease [9]. Activation of the intrarenal RAS promotes systemic hypertension and promotes activation of the sympathetic nervous system and sensitivity to the effects of noradrenaline in the kidney [32]. Ang II-mediated renal hypertrophy also contributes to increased proximal salt reabsorption [33]. The key role of the RAS in promoting systemic hypertension associated with diabetes is illustrated by studies showing that new-onset hypertension in patients with Type 2 diabetes may be prevented by blockade of the RAS [34].

Among the earliest changes in the diabetic kidney are an increase in efferent arteriolar tone leading to an increase in intracapillary pressure and a loss of autoregulation [35]. Early work by Zatz and colleagues showed that a reduction in intraglomerular hydraulic pressure slowed the development of kidney disease in streptozotocin-treated diabetic animals, effectively linking hemodynamic changes in the glomerulus and progressive diabetic nephropathy [35]. One of the most important mediators of this altered hemodynamic response is the RAS. Blockade of the RAS selectively reduces efferent arteriolar tone, thereby reducing glomerular capillary pressure and hemodynamic 'stress' on the glomerulus [36]. This action has been used to explain why, at least in experimental diabetes, RAS blockade appears to be more efficacious in preventing renal injury when compared with similar BP reduction.

However, the renal actions of Ang II in diabetes are not limited to hemodynamic effects. Considerable experimental evidence exists for a direct role of the RAS in kidney injury. Ang II is also an important stimulus for inflammation, oxidative stress and fibrogenesis in the kidney. For example, Ang II triggering the expression and release of the profibrogenic regulator, TGF-β1 and connective tissue growth factor

in the kidney [37]. The primacy of the RAS in diabetes-associated pathology is elegantly illustrated by studies in rat mesangial cells, in which glucose-induced TGF-β1 secretion is completely abrogated by AT_1 receptor blockade [38]. Additionally, Ang II influences a range of other known pathogenic mediators in the diabetic kidney, such as protein kinase C and the inflammatory regulator, nuclear transcription factor, NF-κB and the accumulation of advanced glycation end-products. By contrast, inhibition of the RAS in experimental diabetes is associated with reduced renal cytokine expression, inhibition of protein kinase C and reduced advanced glycation end-product accumulation. Ang II may also directly act to inhibit matrix metalloprotease activity, leading to augmented matrix accumulation [38]. This reduced matrix degradation in diabetic kidney disease may be restored by blockade of the RAS, implying a key role for Ang II in modulating matrix turnover in diabetes [39].

The formation of reactive oxygen species (ROS), as a result of oxidative stress, is also recognized as a key component in the development of diabetic kidney disease. ROS are directly cytotoxic and upregulate inflammation and fibrosis. The expression and activity of NADPH oxidase represents the major source of ROS in the diabetic kidney. NADPH oxidase is directly activated by Ang II, following activation of the AT_1 receptor [40]. This pro-oxidant action may also contribute to the renal consequences of activation of the AT_1 receptor, and therein the benefits arising from its blockade in the setting of diabetic kidney disease.

BP-independent renoprotective effects of RAS blockade

From the above physiological rationale, early blockade of the RAS in patients with diabetes would seem both logical and necessary for the prevention of progressive kidney disease. Such observations have directly led to studies that aimed to specifically explore the utility of RAS blockade beyond blood-pressure lowering in patients with diabetes. However, these studies have largely failed to demonstrate a clear and independent efficacy for the primary prevention of microalbuminuria. In one study of 200 normotensive patients with normoalbuminuria, treatment with the ACE inhibitor, perindopril (2 mg/day), for 4 years, saw a reduction in the development of microalbuminuria, despite having a neutral effect on mean systolic BP [41]. Against this, the Renin–Angiotensin System Study treated 285 normotensive patients with Type 1 diabetes and normoalbuminuria with either the ACE inhibitor, enalapril (20 mg/day), the ARB losartan (100 mg/day) or placebo and followed them for 5 years. Interestingly, more, not less patients treated with the ARB, losartan, progressed to microalbuminuria, than was the case in patients randomized to receive placebo treatment (17 vs 4%; log rank $p = 0.02$). Patients randomized to receive the ACE inhibitor, enalapril, also showed no advantage over placebo (6 vs 4%; p = not significant). Changes in the fraction of glomerular volume occupied by mesangium, a histological marker of diabetic kidney disease quantified on renal biopsy material, were also no different between treatment and placebo groups [42].

A number of studies have also explored the hypothesis that inhibition of the RAS in patients with Type 2 diabetes has additional benefits on kidney disease, beyond blood-pressure lowering. However, like those in Type 1 diabetes, these data are mixed and variable. The UKPDS demonstrated that tight blood-pressure control, whether achieved by an ACE inhibitor or by β-blockers, was associated with a 29% reduction in the risk of microalbuminuria ($p < 0.009$) but the study was not powered to detect between-drug differences [43]. In the FACET fosinipril (20 mg/day) and amlodipine (10 mg/day) were compared in patients with hypertension and Type 2 diabetes, showing no independent protective action of ACE inhibition. Similarly, in the Type 2 diabetes arms of the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes, Micro-HOPE and DIRECT studies, no renoprotective advantages of RAS blockade were observed, despite lower achieved BPs. Put together with observational findings in a meta-analysis, Casas *et al* controversially concluded that ACE or ARBs provided no renoprotective effect beyond BP control [44]. This study has been widely criticized because of 'methodological flaws' and, in particular the inclusion of *post hoc* renal data from the ALLHAT study, which because of its size, dominated the outcomes analysis. Nonetheless, its conclusions were consistent with the then-available data, and subsequent analyses have not overturned these controversial findings.

While subsequent clinical studies have observed positive effects from RAS blockade,

many of these studies deliberately included hypertensive patients. For example, the Bergamo Nephrologic Diabetes Complications Trial in hypertensive patients with Type 2 diabetes did find that the risk of developing microalbuminuria was reduced by half following the use of the ACE inhibitor, trandolapril (2 mg/day), but not by the calcium channel antagonist, verapamil (240 mg/day), despite equivalent BP reduction. Again, the intervention was particularly effective in patients with the highest BPs, which determined the majority of its overall effect in this trial. Similarly, in the recently published Randomized Olmesartan and Diabetes Microalbuminuria Prevention study, the ARB, olmesartan (40 mg/day) reduced the development of microalbuminuria by 15% in mildly hypertensive patients with Type 2 diabetes, beyond that observed in the placebo arm [45]. However, blood-pressure levels were slightly lower in the olmesartan-treated group than in the placebo-treated group (126 vs 129 mmHg), so the question as to whether RAS blockade has truly blood-pressure independent actions on the development of diabetic renal disease effectively remains unanswered. In addition, treatment with olmesartan was associated with a paradoxical increase in cardiovascular deaths, specifically in patients with established cardiovascular disease, leading to the suggestion that this stratagem, although renoprotective, may have significant drawbacks. Olmesartan (10–40 mg/day) also was associated with increased cardiac deaths in the Olmesartan Reducing Incidence of End stage renal disease in diabetic Nephropathy Trial [46], suggesting this may not have been a chance finding. However, given the morbidity and excess mortality associated with CKD, it is likely that the renoprotective efficacy of this intervention will become more the important feature in the long run.

Conclusion

Data from observational and clinical trials demonstrate the importance of BP in the development of diabetic kidney disease. Blood-pressure control will reduce the incidence of kidney disease in patients with diabetes, especially in hypertensive patients. This appears to be the case no matter how it is achieved. Consequently, most guidelines currently recommend the aggressive management of hypertension in diabetic individuals without kidney disease, with or without RAS blockade [1]. Whether RAS blockade offers additional benefits for primary prevention over-and-above blood-pressure control, remains contentious. At best, any 'independent effects' on primary prevention achieved by RAS blockers beyond blood-pressure lowering are modest, and certainly not the panacea envisaged by many practitioners.

Some of the failure of trials of RAS blockade to consistently demonstrate prevention of microalbuminuria may relate to the variable doses, timing and efficacy of agents used in trials. Certainly, some studies have used insufficiently low doses of ACE inhibitor or ARBs to achieve effective RAS blockade and renoprotection. This may be important as the renoprotective effects of RAS blockade in diabetic patients with CKD appears to be dose dependent, over and above blood-pressure lowering [3]. However, such a hypothesis has not been formally tested in diabetic patients without CKD.

Another contributing factor to the apparent lack of additional efficacy of RAS blockade may also be statistical power. Individually, almost all trials that have been undertaken are underpowered (too small with too few events) to evaluate incident microalbuminuria. Moreover, the largest studies are generally *post-hoc* analyses, which when combined with small underpowered trials in meta-analyses may lead to distorted conclusions. In effect, this means that there is no definitive evidence, one way or the other.

This does not mean RAS blockade has no role. On the contrary, given the better tolerability, efficacy and side-effects profile of RAS blockers over other antihypertensive agents [31], as well as added beneficial effects on retinopathy [23] and cardiovascular disease [47], most patients with diabetes without CKD currently receive RAS blockers as first-line antihypertensive agents. Indeed, most patients will initially or ultimately need combination antihypertensive therapy to control their BP, in which case RAS blockade will almost always be utilized in routine clinical practice. This is not incorrect. However, the reason for doing so must be more than any direct actions for the primary prevention of microalbuminuria.

Future perspective: a better blockade of the RAS

Over the next decade many more ACE inhibitors and ARBs will come off patent. This will mean the costs of such therapy will fall and more generic compounds will become available. As such the cost:benefit ratio of these agents will

further improve. There appears to be no advantage or need for any new agents of this class, thus, the future of RAS blockade must be to build a smarter, more sustained blockade in combination with other agents.

The RAS is a homeostatic regulator that relies on feedback regulation to achieve and sustain the delicate balance required for vascular function. However, this feedback regulation is intrinsically antagonistic to the therapeutic goal of blocking the RAS **(Figure 3)**. For example, the suppression of plasma Ang II and aldosterone concentrations by ACE inhibitors is in practice rather weak, variable and unsustained [48–50]. In fact, up to half the patients treated with ACE inhibitors there will be a paradoxical overshoot in aldosterone concentrations 12 months after treatment commences [51,52]. This escape phenomenon also occurs with ARBs possibly due to activation of the AT_2 receptor [53]. Indeed equal rates of elevated aldosterone levels are observed among subjects on ACE inhibitors, ARBs, or a combination of both [53], which may explain the lack of additive effect observed in some clinical studies.

In order to achieve the best renoprotective outcomes using RAS blockade there has been a recent focus on a way to circumvent the 'escape' and achieve sustained reductions in Ang II [54,55]. One approach has been to block the feedback induction of renin, using orally active selective renin inhibitors, such as aliskiren, SPP635, SPP676 and SPP1148. These agents specifically inhibit the enzymatic cleavage of angiotensinogen to Ang I, and induce a dose–dependent and sustained decrease in Ang II tissue and plasma levels [56]. Selective renin inhibition is able to achieve blood-pressure lowering comparable (but no better than) ARBs and ACE inhibitors in hypertensive individuals [56]. Consequently, most studies have looked at the potential for combination of ACE inhibitions or ARBs with renin inhibitors, where feedback renin overactivity potentially attenuates their utility as monotherapies. Certainly, better blood-pressure control can be achieved with combination therapy [57]. In addition, although not a primary prevention study, the AVOID trial treated 599 hypertensive patients with Type 2 diabetes and nephropathy with the renin inhibitor, aliskiren (150 mg daily titrated to 300 mg daily) after 3 months or placebo added to the ARB, losartan (100 mg/day) for over 6 months. In this study, there was a significant fall in proteinuria (~20%) and a reduced incidence of renal impairment in patients receiving aliskiren [58]. Similar additive antiproteinuric effects have been reported when aliskiren has been used in combination with the ARB, irbesartan [59].

As yet this strategy has not been tested in the primary prevention of nephropathy, although a rationale is quite clear and will almost certainly be studied *post hoc*. Whether the feedback induction of prorenin that occurs following inhibition of its enzymatic activity is able to independently induce signaling pathways via the prorenin receptor currently remains to be established, although some researchers have variously reported renal dysfunction, inflammation and oxidative stress induced by prorenin in experimental models. At the same time, blockade of prorenin signaling may be vasculoprotective in experimental diabetes.

Another strategy to re-emerge as a potential therapeutic candidate may be to combine RAS blockers with agents that prevent aldosterone binding to mineralocorticoid receptors, such as spironolactone and eplerenone. Some (but not all) studies suggest this combination may have additional renoprotective actions in patients with established nephropathy [60]. However, it is unclear whether the benefits of combination therapy are specifically enhanced in patients with aldosterone escape, or simply because of better blood-pressure control with enhanced diuresis. There may also be unforeseen problems with combination therapy, with one study reporting higher levels of Ang II and an increased incidence

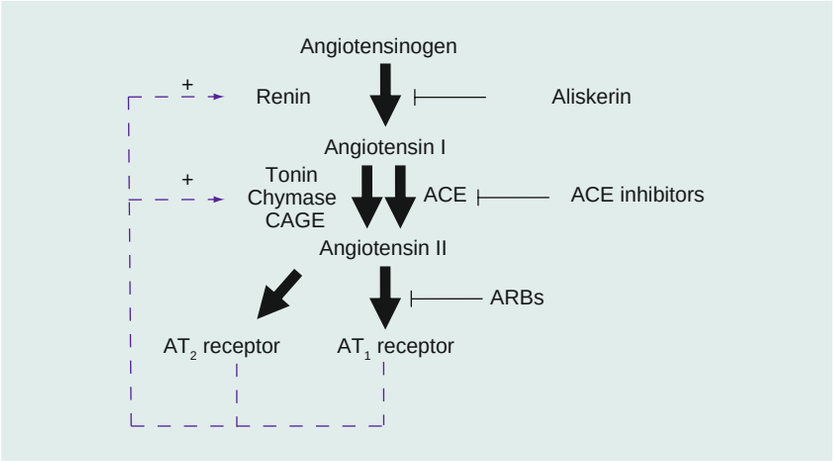

Figure 3. Feedback regulation of the renin–angiotensin system. Activation of homeostatic feedback pathways (dashed line) means that effective blockade of the renin–angiotensin system and suppression of aldosterone synthesis can be escaped.
ARB: Angiotensin receptor blocker.

of escape in patients receiving spironolactone in combination with conventional RAS blockade [61]. Hyperkalemia is also a major adverse effect, particularly in patients with comorbid cardiac disease or kidney disease who rely on aldosterone for potassium balance. Given these risks and the lack of interest of clinical trials using 'older' drugs such as aldosterone, it is unlikely that such dual or triple blockade has much of a future, except as a benchmark for renin inhibition.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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