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Slowing the Progression of Adult Chronic Kidney Disease

Therapeutic Advances

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Abstract

When kidney disease of any aetiology results in substantial loss of nephrons, a common clinical syndrome, characterised by hypertension, proteinuria and a progressive decline in renal function, ensues. This observation suggests that common mechanisms may contribute to progressive renal injury and that therapeutic interventions that inhibit these common pathways may afford renal protection. Research to date has identified several mechanisms that may contribute to progressive renal injury including glomerular haemodynamic changes, multiple effects of angiotensin II and detrimental effects of excessive filtration of plasma proteins by injured glomeruli. Clinical trials over the past decade have identified several interventions that are effective in slowing the rate of progression of chronic kidney disease (CKD). The use of ACE inhibitors, angiotensin receptor

antagonists or a combination of the two should be regarded as fundamental to any therapy for slowing the rate of CKD progression. Hypertension should be treated aggressively to achieve a blood pressure target of <130/80mm Hg. Reduction of proteinuria to <0.5 g/day should be regarded as an independent therapeutic goal. Although inconclusive, there is some evidence to support moderate dietary protein restriction to 0.6 g/kg/day in appropriate patients. Hyperlipidaemia may contribute to CKD progression and should be treated to reduce cardiovascular risk and potentially improve renal protection. Smoking cessation should be encouraged and, where necessary, assisted. Among diabetic patients tight glycaemic control should be achieved (glycosylated haemoglobin <7%). These interventions are simple and relatively inexpensive. If applied to all patients with CKD they will result in substantial slowing of renal function decline in many patients and thereby reduce the number who progress to end-stage renal disease and require renal replacement therapy.

The provision of long-term dialysis treatment represents a growing problem for healthcare systems worldwide. In developing countries this expensive form of therapy for a limited number of patients competes for funding with the primary healthcare needs of the population and in wealthy countries there is concern over the escalating costs of dialysis provision. Moreover, long-term dialysis is associated with annual mortality rates of up to 20% and substantial morbidity for individual patients.[1] Thus, there is an urgent need for action to reduce the number of patients who are dependent on dialysis. In this context it is important to emphasise that the majority of cases of end-stage renal disease (ESRD) result from chronic kidney disease (CKD) that produces progressive injury to the kidneys over several years. This implies that in many patients the need for dialysis could be delayed or even prevented by interventions that slow the rate of decline in renal function. This article reviews recent developments in the field of renal protective therapy and proposes a simple but comprehensive strategy for significantly slowing the rate of CKD progression.

1. Mechanisms Underlying the Progression of Chronic Kidney Disease (CKD)

It has been appreciated for several decades that despite the wide range of pathological processes that may produce renal injury, substantial loss of functioning nephrons provokes a common syndrome. This syndrome is characterised by systemic hypertension, proteinuria and a progressive decline in glomerular filtration rate (GFR), the rate of which depends more upon individual patient characteristics than specific disease aetiology. These observations suggest that CKD progresses via a common pathway of mechanisms and that therapeutic interventions inhibiting this pathway may slow the rate of progression of CKD irrespective of the initiating cause.

1.1 Glomerular Capillary Haemodynamics

When rats are subjected to surgical ablation of five-sixths of their renal mass, they develop hypertension, proteinuria and a progressive loss of GFR, features similar to those of human CKD. Therefore, this model has been utilised extensively in the study of mechanisms of CKD progression. Hostetter et al.[2] showed experimentally that when nephrons were lost, remaining glomeruli undergo haemodynamic adaptations resulting in substantial increases in single nephron GFR (SNGFR) and glomerular capillary hydraulic pressure (P_{GC}) that allow partial compensation for the decrease in total GFR. Furthermore, the observation of structural injury to glomerular cells as early as 1 week after five-sixths nephrectomy suggests that these haemodynamic changes, although initially adaptive, eventuate in glomerular damage that results in a further loss of

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nephrons, thereby establishing a vicious cycle of progressive renal injury.[2]

Experimental studies supported this hypothesis by showing that attenuation of the glomerular haemodynamic changes resulted in protection of remnant kidneys from progressive injury. Low protein diet feeding normalised SNGFR as well as P_{GC} and afforded substantial protection from glomerular injury.[2] Treatment with an ACE inhibitor had little effect on SNGFR but did normalise P_{GC} and resulted in significant renal protection, suggesting that P_{GC} rather than SNGFR was the critical determinant of glomerular injury in the remnant kidney.[3] Moreover, treatment with a combination of hydralazine, hydrochlorothiazide and reserpine was associated with similar lowering of systemic blood pressure to ACE inhibitor, but did not lower P_{GC} or afford renal protection. Micropuncture studies in a rodent model of diabetic nephropathy showed that glomerular hypertension and hyperfiltration are also present in this form of CKD. The importance of these haemodynamic factors in the complex pathogenesis of diabetic nephropathy was confirmed by experimental studies, which showed that normalisation of P_{GC} by low protein diet[4] or treatment with an ACE inhibitor[5] prevented renal injury despite persistent hyperglycaemia.

1.2 Abnormal Ultrafiltration of Plasma Proteins

There is now a large body of evidence to support the notion that the abnormal filtration of plasma proteins by diseased glomeruli initiates further mechanisms that contribute to renal injury. Proximal tubule cells normally reabsorb small proteins that appear in glomerular ultrafiltrate but *in vitro* studies have found that tubule cells exposed to high concentrations of large plasma proteins produce several proinflammatory molecules including endothelin-1, cytokines and chemokines, which are secreted from the basolateral aspect of the cells.[6] It is proposed that these molecules stimulate interstitial inflammatory cell recruitment that eventuates in tubulointerstitial fibrosis. Thus, proteinuria may provide the link between glomerular injury and subsequent tubulointerstitial fibrosis. Furthermore, experimental evidence suggests that increased ultrafiltration of proteins results in accumulation of proteins within podocytes. Subsequent podocyte injury is associated with increased expression of transforming growth factor (TGF)-β that may further contribute to glomerulosclerosis.[7] Several clinical studies have confirmed the importance of abnormal protein traffic by showing strong associations between the severity of proteinuria and progression of CKD (see section 2.2).

1.3 Angiotensin II

Angiotensin II has been identified as an important mediator of the glomerular haemodynamic changes associated with progressive renal injury. In addition, experimental studies in isolated perfused kidneys indicate that angiotensin II may contribute to the pathogenesis of proteinuria by directly increasing glomerular permeability to macromolecules. These changes were prevented by pre-treatment with an angiotensin II receptor antagonist.[8] Further experimental studies have revealed several other non-haemodynamic effects of angiotensin II that may also be important in CKD progression. These include: (i) mesangial cell proliferation and induction of TGFβ expression; (ii) stimulation of plasminogen activator inhibitor-1 production by endothelial and vascular smooth muscle cells; (iii) macrophage activation and increased phagocytosis; and (iv) adrenal production of aldosterone, recently recognised as a mediator of renal injury.[9] Thus, angiotensin II appears to play a central role in several of the mechanisms contributing to progressive renal injury and is a logical target for interventions to slow CKD progression.

A detailed discussion of all of the mechanisms that may contribute to progressive renal injury is beyond the scope of this article. Since not all experimental models support a central role for glomerular haemodynamic changes, there has in the past been considerable debate regarding the relative importance of haemodynamic and non-haemodynamic mechanisms. Recently, a consensus view has emerged, which incorporates both into a complex set of

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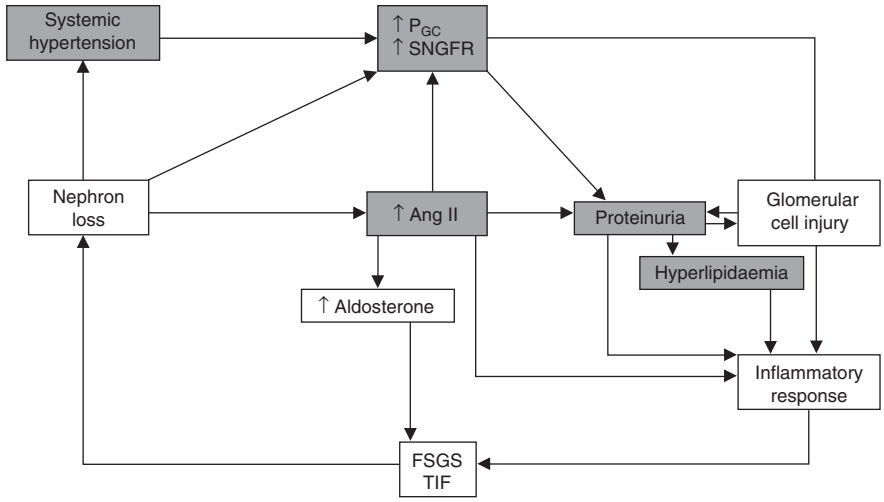

Fig. 1. Schema showing the interaction of multiple mechanisms that contribute to a vicious cycle of progressive nephron loss in chronic kidney disease (CKD). Shaded boxes indicate therapeutic targets for interventions to slow the rate of CKD progression. **Ang II** = angiotensin II; **FSGS** = focal and segmental glomerulosclerosis; **P_{GC}** = glomerular capillary hydraulic pressure; **SNGFR** = single nephron glomerular filtration rate; **TIF** = tubulointerstitial fibrosis; ↑ indicates increase.

interacting mechanisms that together contribute to progressive damage (see figure 1).

2. Therapeutic Interventions for Slowing CKD Progression

2.1 Treatment of Hypertension

Hypertension is an almost universal consequence of CKD and is often the presenting feature. It is clear that accelerated phase hypertension may cause severe renal injury but the extent to which moderate hypertension may be the primary cause of renal damage remains uncertain. Several large epidemiological studies have identified hypertension as an important risk factor for the subsequent development of CKD,[10,11] but this in itself does not prove a causal link. On the other hand, there is compelling evidence that hypertension accelerates the rate of progression of CKD resulting from other causes. In one early study, the rate of decline in GFR was reduced to less than half of baseline by the initiation of antihypertensive treatment with a thiazide diuretic or β-adrenoceptor antagonist in a small cohort of patients with type 1 diabetes mellitus with diabetic nephropathy.[12] Subsequent studies have confirmed these findings in non-diabetic forms of CKD.[13-15] Thus, it is now widely acknowledged that the treatment of hypertension is fundamental to interventions for slowing the rate of CKD progression.

2.1.1 Therapeutic Targets for Blood Pressure

This raises the question of what level of blood pressure control is required for optimal renal protection. Several studies have reported greater lowering of cardiovascular risk with lower blood pressure targets, but to date prospective randomised studies have generally failed to show that setting a lower blood pressure goal is associated with better renal outcomes. However, these findings should be interpreted with caution because of difficulty in achieving adequate differences in blood pressure control between randomised groups and the complexity of the study design in some cases. In the MDRD (Modification of Diet in Renal Disease) study, 840 CKD patients were randomised to a target mean arterial pressure (MAP) of 107mm Hg (140/90mm Hg, 'usual' blood pressure target) or 92mm Hg (125/75mm Hg, 'low' blood pressure target).[16] Whereas the primary analysis did not show any overall difference in the rate of GFR decline, patients randomised to the 'low' blood pressure target evidenced a more

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rapid initial GFR decline, which is likely to be due to associated renal haemodynamic effects that obscured a subsequent slower rate of GFR decline than that observed in the 'usual' blood pressure target group. It is possible that if the study had been continued for a longer period, significant differences in favour of the lower blood pressure target may have emerged. Furthermore, the effect of different blood pressure targets was strongly modulated by the amount of baseline proteinuria. A higher level of proteinuria was associated with a greater difference in GFR decline between 'usual' and 'low' blood pressure target groups. Secondary analysis revealed significant correlations between the rate of GFR decline and achieved blood pressure, an effect that was also more marked among those with greater baseline proteinuria. The investigators conclude by recommending a blood pressure goal of <125/75mm Hg (MAP = 92mm Hg) for CKD patients with >1 g/day of proteinuria, and a goal of <130/80mm Hg (MAP = 98mm Hg) for those with proteinuria of 0.25–1.0 g/day.[17] As these findings are based largely on secondary analyses, it must be conceded that the results of the MDRD study do not provide unequivocal support for the use of lower blood pressure targets.

However, several other lines of evidence do strengthen support for the notion that greater lowering of blood pressure is associated with more effective renal protection. In one prospective study of patients with type 1 diabetes with established nephropathy receiving ACE inhibitor therapy, randomisation to a 'low' (MAP = 92mm Hg) versus 'usual' (MAP = 100–107mm Hg) target blood pressure was associated with significantly lower levels of proteinuria after 2 years, although there was no significant difference in the rate of GFR decline.[18] Furthermore, analysis of data from nine long-term clinical trials involving patients with diabetic and non-diabetic forms of CKD found lower rates of GFR decline among patients with lower achieved blood pressure.[19] Thus, whereas no single study has demonstrated unequivocal benefit for renal protection associated with lower blood pressure targets, the weight of the combined evidence has prompted the American Diabetes Association,[20] US National Kidney Foundation (NKF)[21] and Joint National Committee on Prevention, Detection and Treatment of High Blood Pressure[22] to recommend that blood pressure should be lowered to <130/80mm Hg in all patients with CKD. However, care should be taken to avoid potentially dangerous hypotension in patients with autonomic neuropathy, labile blood pressure or arteriosclerosis (resulting in decreased vascular compliance).

2.1.2 Choice of Antihypertensive

Several factors should be considered in selecting an antihypertensive for the patient with CKD. First, an ACE inhibitor or angiotensin receptor antagonist should be considered first-line therapy for all patients with proteinuria and CKD unless specifically contraindicated (see section 2.3). Secondly, data from the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which appear to support the use of diuretics as first-line therapy for hypertensive patients,[23] should not be extrapolated to patients with CKD. Diuretics are seldom effective as monotherapy in patients with renal impairment. On the other hand, diuretics are useful in achieving blood pressure targets in combination with an ACE inhibitor or angiotensin receptor antagonist. Finally, it should be noted that the dihydropyridine (DHP) class of calcium channel antagonists may have adverse effects on the progression of CKD. In the experimental five-sixths nephrectomy model, DHP calcium channel antagonist treatment allowed greater transmission of systemic blood pressure to the renal microcirculation and was associated with more rapid progression of renal injury than ACE inhibitor treatment.[24]

Whereas one relatively small clinical study found no difference between the renal protective effects of a DHP calcium channel antagonist and an ACE inhibitor,[25] two larger studies[26,27] have reported adverse outcomes associated with the use of DHP calcium channel antagonists. A secondary analysis of data from the REIN (Ramipril Efficacy In Nephropathy) study found that treatment with the DHP calcium channel antagonist nifedipine or amlodipine was associated with higher levels of proteinuria and

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more rapid GFR decline than other antihypertensives in those patients who were not receiving an ACE inhibitor and who did not achieve a MAP of <100mm Hg.[26] In the AASK (African American Study of Kidney Disease and Hypertension),[27] patients with CKD and hypertension were randomised to treatment with an ACE inhibitor or amlodipine or a β-adrenoceptor antagonist and diuretic in combination. The amlodipine arm of the study was stopped prematurely because of a more rapid decline in GFR among these patients versus those receiving the β-adrenoceptor antagonist or ACE inhibitor, particularly among those with >1 g/day of proteinuria. On the basis of this evidence, we recommend that DHP calcium channel antagonists should not be used in patients with CKD unless they are required in combination with ACE inhibitor to achieve blood pressure targets. These concerns do not appear to apply to non-DHP calcium channel antagonists. In one study, when added to ACE inhibitor treatment, non-DHP calcium channel antagonists reduced proteinuria in patients with type 2 diabetes and overt nephropathy.[28]

2.2 Reduction of Proteinuria

As discussed in section 1.2 there is now extensive experimental evidence suggesting that excessive filtration of serum proteins by injured glomeruli and subsequent absorption by tubule and glomerular cells directly contributes to progressive renal damage. Furthermore, clinical studies have found close associations between the severity of proteinuria and the risk of CKD progression. In the REIN study, higher levels of baseline proteinuria were associated with more rapid rates of GFR decline and among patients with initial proteinuria of >3 g/day, ACE inhibitor treatment reduced proteinuria to an extent that correlated inversely with the subsequent rate of GFR decline.[29]

Furthermore, in the MDRD study, a reduction in proteinuria, independent of blood pressure, was associated with slower progression of CKD and the degree of benefit achieved through blood pressure lowering was dependent on the extent of baseline proteinuria.[17] Re-analysis of data from both strata of the REIN study found that the percentage reduction in proteinuria over the first 3 months and the absolute level of proteinuria at 3 months were strong independent predictors of the subsequent rate of decline in GFR.[30] A meta-analysis that included data from 1860 patients with non-diabetic CKD confirmed these findings and showed that during antihypertensive treatment, the current level of proteinuria was a powerful predictor of the combined endpoint of doubling of baseline serum creatinine or onset of ESRD (relative risk 5.56 for each 1.0 g/day of proteinuria).[31] The strong association between the achievement of proteinuria reduction and renal protection in clinical studies implies that minimisation of proteinuria should be regarded as an important independent therapeutic goal in renal protective strategies. Several researchers suggest that therapy should be escalated to reduce proteinuria to <0.5 g/day.[32-34]

2.3 Pharmacological Inhibition of the Renin-Angiotensin System

The publication of several prospective randomised trials that together provide clear evidence of specific renal protective benefits of pharmacological inhibitors of the renin-angiotensin system (RAS) is perhaps the most important development in the treatment of CKD over the past decade (summarised in tables I and II).

2.3.1 ACE Inhibitors

Diabetic Nephropathy

The first large prospective randomised controlled trial to show specific renal protection with ACE inhibitor treatment in human CKD was published in 1993.[35] Patients with type 1 diabetes (n = 409) and established diabetic nephropathy (proteinuria >0.5 g/day; serum creatinine <2.5 mg/dL) were randomised to receive captopril or placebo plus other antihypertensives and doses were adjusted to achieve a blood pressure goal of <140/90mm Hg. Equivalent blood pressure control was achieved in the two groups. After a median follow-up of 3 years, captopril treatment was associated with a 48% reduction in the risk of doubling of serum creatinine

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Table I. Summary of prospective randomised studies that have reported improved preservation of renal function with ACE inhibitor (ACEI) and/or angiotensin receptor antagonist (ARA) treatment in patients with different forms of chronic kidney disease (CKD)

Patients	Treatment	Outcome	References
Type 1 DM + DN	ACEI	50% ↓ risk of dialysis, transplant or death	35
Type 2 DM + DN	ARA	25–37% ↓ risk of creatinine doubling	36,37
		23–28% ↓ risk of ESRD	
Non-diabetic CKD	ACEI	↓ risk of creatinine doubling or ESRD (RR 0.52)	29,38
Non-diabetic CKD	ACEI + ARA	↓ risk of creatinine doubling or ESRD (HR 0.4 vs monotherapy)	39

DM = diabetes mellitus; **DN** = diabetic nephropathy; **ESRD** = end-stage renal disease; **HR** = hazard ratio; **RR** = relative risk ratio; ↓ indicates decreased.

and a 50% reduction in the risk of the combined endpoint of death, dialysis and renal transplantation.

This important study led investigators to ask whether ACE inhibitor treatment may also benefit patients with type 1 diabetes who are at increased risk of developing nephropathy as evidenced by the presence of microalbuminuria. A meta-analysis of 12 studies, including 689 patients, found that ACE inhibitor treatment was associated with a significant reduction in the risk of progression to overt nephropathy (odds ratio 0.38).[40] The question of whether or not ACE inhibitor treatment is of specific benefit among patients with type 1 diabetes with no hypertension or albuminuria remains unanswered. A subgroup analysis of such patients in the EUCLID (EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes) study found that ACE inhibitor treatment reduced albuminuria by 12.7%, but this trend was not statistically significant.[41]

The evidence base for renal protective effects of ACE inhibitor treatment in patients with type 2 diabetes is unfortunately rather weak. Only one study[53] has reported a greater reduction in GFR decline associated with ACE inhibitor versus other antihypertensive therapy among patients with type 2 diabetes with overt nephropathy and others have found no additional benefit.[54-56] On the other hand, several studies have reported that ACE inhibitor treatment decreased microalbuminuria[43-46] or reduced the number of patients progressing from microalbuminuria to overt nephropathy (risk reduction 24–67%)[47-49] and one study found a small beneficial effect (absolute risk reduction of 12.5%) of ACE inhibitor treatment in preventing microalbuminuria in normotensive patients with type 2 diabetes.[50] In contrast, one relatively large study found no renal protective benefit of ACE inhibitor over β-adrenoceptor antagonist treatment among hypertensive patients with type 2 diabetes with normo- or microalbuminuria.[42]

On the basis of these data, ACE inhibitor treatment should be regarded as first-line treatment for all patients with type 1 diabetes with microalbuminuria or overt nephropathy. At present there are insufficient data to support the specific use of ACE inhibitors in patients with type 1 diabetes without

Table II. Summary of prospective randomised studies examining the effect of ACE inhibitor (ACEI) and/or angiotensin receptor antagonist (ARA) treatment on microalbuminuria in diabetic patients

Patients	Treatment	Outcome	References
Type 1 DM + MA	ACEI	↓ risk of overt nephropathy (OR = 0.38)	40
Type 1 DM + NA	ACEI	12.7% ↓ in albuminuria (NS)	41
Type 2 DM + MA	ACEI	24–67% ↓ risk of overt nephropathy[a]	43-49
Type 2 DM + NA	ACEI	12.5% ↓ risk of developing MA[a]	50
Type 2 DM + MA	ARA	↓ risk of overt nephropathy (HR 0.30)	51
Type 2 DM + MA	ACEI + ARA	Greater ↓ in BP and urine ACR vs monotherapy	52

a One study showed no benefit.[42]

ACR = albumin : creatinine ratio; **BP** = blood pressure; **DM** = diabetes mellitus; **HR** = hazard ratio; **MA** = microalbuminuria; **NA** = normoalbuminuria; **NS** = not significant; **OR** = odds ratio; ↓ indicates decreased.

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microalbuminuria. Published studies do not show consistent benefit with ACE inhibitor treatment in patients with type 2 diabetes with established nephropathy but this may be due to a lack of adequately powered studies. However, there is sufficient evidence to recommend ACE inhibitor treatment for reducing the rate of progression from microalbuminuria to overt nephropathy in patients with type 2 diabetes. Finally, it should be remembered that cardiovascular disease is the most common cause of morbidity and mortality among patients with type 2 diabetes. The finding in the HOPE (Heart Outcomes Prevention Evaluation) study of a 25% reduction in the combined primary endpoint of myocardial infarction, stroke or cardiovascular death in ramipril-treated patients with type 2 diabetes with risk factors for cardiovascular disease[46] indicates that ACE inhibitor treatment should be considered as an intervention for reducing cardiovascular risk in these patients.

Non-Diabetic CKD

The substantial benefits observed in diabetic patients prompted similar studies to investigate the potential renal protective effects of ACE inhibitor in non-diabetic forms of CKD. One early study reported a 53% reduction in the risk of reaching the combined endpoint of doubling of baseline serum creatinine or the need for dialysis with ACE inhibitor treatment. However, a significantly lower blood pressure among patients receiving ACE inhibitor versus placebo made it impossible to separate the beneficial effects of lowering blood pressure from any unique effects of ACE inhibitor treatment.[57]

This problem was addressed by the REIN study, in which 352 patients with non-diabetic CKD were randomised to ACE inhibitor or placebo plus other antihypertensives to achieve similar blood pressure control. Among patients with ≥3 g/day of proteinuria at baseline, a significantly lower rate of decline in GFR per month was observed in patients receiving the ACE inhibitor (0.53 vs 0.88 mL/min) at the second interim analysis and the study was discontinued early.[29] Further analysis showed a significant reduction in the risk of the combined endpoint of a doubling of serum creatinine or ESRD in the ACE inhibitor group (risk ratio 1.91 for the placebo group).[29] Similar findings were subsequently reported for REIN study patients with 1–3 g/day of proteinuria in whom ACE inhibitor treatment significantly reduced the incidence of ESRD (relative risk for placebo group 2.72), particularly among those with a GFR of <45 mL/min at baseline.[38] A meta-analysis of 11 studies, including 1860 patients with non-diabetic CKD, reported that antihypertensive treatment that included an ACE inhibitor resulted in greater lowering of blood pressure and proteinuria.[58] Even after statistical adjustment for these factors, ACE inhibitor treatment was associated with significantly lower risks of reaching ESRD (relative risk 0.69; 95% CI 0.51, 0.94), suggesting that ACE inhibitor treatment afforded renal protection in addition to its antihypertensive effects. Moreover, the benefit of ACE inhibitor treatment was greater in patients with higher levels of baseline proteinuria.

One recent study has provided the first evidence of renal protection with ACE inhibitor treatment in a group of patients with CKD due to a single form of glomerulonephritis, IgA nephropathy. Patients (all with proteinuria >0.5 g/day) randomised to ACE inhibitor treatment showed a reduction in proteinuria and a significantly lower incidence of the primary endpoint, a 50% increase in serum creatinine.[59]

In summary, there is now clear evidence that ACE inhibitor treatment affords renal protection in patients with non-diabetic CKD and proteinuria. As discussed in the Diabetic Nephropathy subsection of section 2.3.1, data from the HOPE study imply that ACE inhibitor treatment should also be considered as an intervention to reduce cardiovascular risk among non-diabetic CKD patients.[60]

2.3.2 Angiotensin Receptor Antagonists

Angiotensin receptor antagonists inhibit the RAS by blocking angiotensin II subtype 1 (AT_1) receptors. Thus ACE inhibitors and angiotensin receptor antagonists have different effects on the RAS, and these differences may be therapeutically relevant. ACE inhibitors inhibit only ACE-dependent angiotensin II production, whereas angiotensin receptor

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antagonists block the effect of angiotensin II from any source at the receptor level. This may be important because in the presence of ACE inhibitor treatment the inhibition of angiotensin II formation may be bypassed by other proteases, including chymase and other serine proteases.[61] There are at least two types of the angiotensin II receptors, and blockade of AT_1 receptors in the presence of elevated angiotensin II levels will therefore cause stimulation of angiotensin II subtype 2 (AT_2) receptors. Whereas AT_1 receptors mediate most of the known effects of angiotensin II, including vasoconstriction, stimulation of aldosterone synthesis and release, and renal tubule sodium and water reabsorption, the role of AT_2 receptors is not clearly defined. Nevertheless, ongoing stimulation of AT_2 receptors may in theory have beneficial effects (reviewed by Taal and Brenner[9]). Despite these theoretical differences, experimental studies in different CKD models have found that ACE inhibitors and angiotensin receptor antagonists afford equivalent renal protection.[9]

Several large randomised studies have established a clear role for angiotensin receptor antagonists as renal protective therapy in patients with type 2 diabetes. In the RENAAL (Reduction of Endpoints in NIDDM with Angiotensin II Antagonist Losartan) trial, 1513 patients with established diabetic nephropathy were randomised to losartan or placebo treatment plus additional antihypertensives to achieve equivalent blood pressure control.[36] Losartan treatment was associated with a 35% reduction in proteinuria and a lower incidence of doubling of baseline serum creatinine (risk reduction 25%) or ESRD (risk reduction 28%). The IDNT (Irbesartan Diabetic Nephropathy Trial) randomised 1715 similar patients to treatment with irbesartan, amlodipine or placebo.[37] Irbesartan treatment was associated with a 33% lower risk of a doubling of baseline serum creatinine versus placebo and a 37% reduction versus amlodipine. Although not statistically significant, irbesartan treatment yielded a 23% reduction in the risk of ESRD versus placebo and amlodipine. The close matching of achieved blood pressure between groups in these trials implies that the additional renal protection afforded by angiotensin receptor antagonist treatment was not due to their antihypertensive effects alone.

Angiotensin receptor antagonist treatment also appears to be of benefit in patients with type 2 diabetes with microalbuminuria. In one study, 590 patients with type 2 diabetes with hypertension and microalbuminuria were randomised to two different dosages of irbesartan (150 or 300 mg/day) or placebo.[51] The incidence of overt proteinuria was significantly different among the groups (5.2% vs 9.7% vs 14.9%) and the higher dose of irbesartan was associated with a substantial reduction in the risk of developing overt nephropathy (hazard ratio 0.30 vs placebo). However, this benefit was associated with significantly lower blood pressures in the irbesartan groups. Nevertheless, the risk reduction was similar after adjustment for the baseline level of microalbuminuria and blood pressure. In a similar study, 332 patients with microalbuminuria (with or without hypertension) were randomised to treatment with valsartan or amlodipine and dosages adjusted to achieve equivalent blood pressure control.[62] Valsartan treatment lowered albuminuria significantly more than amlodipine and more patients receiving valsartan reverted to normal albuminuria (29.9% vs 14.5%).

It is interesting to note that the degree of renal protection achieved with angiotensin receptor antagonist treatment appears to be relatively less than that reported with ACE inhibitor treatment. This may be explained by differences in trial design, particularly with respect to patient selection (patients with type 1 diabetes and patients with non-diabetic CKD in the ACE inhibitor trials; patients with type 2 diabetes in the angiotensin receptor antagonist trials), or to intrinsic differences in efficacy. Unfortunately, large clinical studies directly comparing the renal protective efficacy of ACE inhibitor and angiotensin receptor antagonist treatment have not been conducted. It seems unlikely that pharmaceutical companies will be willing to sponsor such studies because of the loss of patent protection on ACE inhibitors.[63] One important advantage of angiotensin receptor antagonists over ACE inhibitors is their more favourable adverse

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effect profile. In clinical trials, angiotensin receptor antagonists have been reported to have adverse effect profiles similar to placebo.[64,65] Importantly, angiotensin receptor antagonists are not associated with the cough that may occur in up to 20% of patients receiving ACE inhibitors. Among patients converted from ACE inhibitor to angiotensin receptor antagonist therapy, recurrence of a cough was significantly lower than in patients rechallenged with an ACE inhibitor.[66,67] Thus, even in the absence of clinical trials in type 1 diabetes or non-diabetic CKD, available evidence supports the use of angiotensin receptor antagonists as an alternative in patient groups who are unable to tolerate ACE inhibitors because of adverse effects.

2.3.3 Combination ACE Inhibitor and Angiotensin Receptor Antagonist Therapy

The differing effects of ACE inhibitors and angiotensin receptor antagonists on the RAS imply that in combination they can be expected to produce more complete inhibition of the RAS, which may in turn afford more effective renal protection. Unfortunately, the added antihypertensive effects of combination therapy have made it difficult to separate the benefits of additional blood pressure lowering from benefits directly attributable to dual blockade of the RAS. In one study, 60 patients with CKD had candesartan cilexetil added to maximum dose ACE inhibitor therapy in a randomised crossover protocol.[68] Combination therapy resulted in greater lowering of blood pressure and greater reductions in proteinuria than ACE inhibitor treatment. Similarly, in a pilot study designed to investigate the safety of combination therapy, 108 patients were randomised to treatment with valsartan or two different doses of valsartan plus benazepril and followed up for 4 or 5 weeks.[69] Combination therapy resulted in greater blood pressure reduction and greater reductions in proteinuria than monotherapy.

On the other hand, two studies have shown renal protective benefit with combination therapy in the absence of additional blood pressure lowering. In the COOPERATE trial, 263 patients with non-diabetic CKD were randomised to treatment with trandolapril, losartan or a combination of both.[39] Prior to initiation of the study treatment, blood pressure was intensively controlled with antihypertensive agents other than ACE inhibitor or angiotensin receptor antagonist. If patients became hypotensive with the addition of the study medication, the dose of the other antihypertensives was reduced. The study was halted early because of a clear advantage associated with combination therapy that resulted in significantly greater reductions in proteinuria (−75.6% vs −42.1% with losartan and −44.3% with trandolapril) and significantly lower incidence of the primary endpoint (doubling of serum creatinine or ESRD; hazard ratio 0.4). These benefits could be specifically attributed to combination therapy because there was no difference in achieved blood pressure between the groups. In a smaller study, 24 patients with non-diabetic CKD were treated with ACE inhibitor or angiotensin receptor antagonist versus combination therapy in a crossover design.[70] Despite similar changes in blood pressure, combination therapy reduced proteinuria to a greater extent than monotherapy.

Combination therapy has also been studied in patients with diabetic nephropathy. The CALM (Candesartan And Lisinopril Microalbuminuria) study included 199 hypertensive patients with type 2 diabetes with microalbuminuria, randomised first to ACE inhibitor or angiotensin receptor antagonist therapy and then, after 12 weeks, to combination therapy or continued monotherapy.[52] Combination therapy afforded greater reductions in blood pressure and albuminuria than either treatment alone. Two smaller studies have examined effects in patients with established diabetic nephropathy. Among 21 patients with type 1 diabetes with proteinuria >1 g/day and continued hypertension despite ACE inhibitor treatment, addition of the angiotensin receptor antagonist irbesartan resulted in a mean 8/5mm Hg reduction in blood pressure and a further 37% reduction in albuminuria.[71] Similarly, among 18 patients with type 2 diabetes with proteinuria and hypertension despite ACE inhibitor treatment, addition of candesartan cilexetil resulted in a 10mm Hg reduction in systolic blood pressure and a 25% reduction in albuminuria.[72]

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Table III. Interventions for minimising the risk of adverse events with ACE inhibitor (ACEI) and angiotensin receptor antagonist (ARA) treatment in patients with chronic kidney disease

Exclude renovascular disease
Optimise K^+ control: dietary restriction, avoid K^+ supplements, stop potassium-sparing diuretics
Avoid hypovolaemia: stop diuretics 2–3 days prior to starting ACEI or ARA treatment
Stop NSAIDs
Start with lowest dose: titrate dose up with frequent monitoring
Monitor serum creatinine and K^+: before starting and after each dose increase

In summary, the majority of studies to date have found that combination ACE inhibitor and angiotensin receptor antagonist therapy reduces blood pressure and proteinuria to a greater extent than monotherapy. The question of whether this combination is superior to any other combination of ACE inhibitor and other antihypertensives is unanswered. On the other hand, the COOPERATE study[39] and one smaller study[70] reported clear benefit associated with combination therapy that was not attributable to any additional antihypertensive effect. Although further studies are required to better identify which patients will benefit from combination therapy, we recommend that it should be considered in CKD patients who have not achieved therapeutic goals for blood pressure and proteinuria reduction with ACE inhibitor or angiotensin receptor antagonist monotherapy.

2.3.4 ACE Inhibitors and Angiotensin Receptor Antagonists: Safety Considerations

Some physicians are reluctant to prescribe ACE inhibitors or angiotensin receptor antagonists in CKD patients because of legitimate concerns about a potential rise in serum creatinine or potassium. However, clinical trials have shown that if simple precautions are taken (summarised in table III) these complications are rare. Discontinuation of therapy because of uncontrolled hyperkalaemia has been reported in only 0–4% of patients and the overall incidence was no different in ACE inhibitor- versus non-ACE inhibitor-treated patients when data from six studies were combined.[73] Nevertheless, it is important to minimise the risk of hyperkalaemia prior to initiating ACE inhibitor or angiotensin receptor antagonist therapy by discontinuing potassium supplements and avoiding potassium-sparing diuretics and high-potassium foods. Serum electrolytes should be checked before starting treatment to ensure that the potassium is not elevated. Similarly, a progressive rise in serum creatinine is seldom seen in patients without bilateral renal artery stenosis (in whom ACE inhibitor and angiotensin receptor antagonist are contraindicated). Moreover, it is important to appreciate that an initial increase in serum creatinine probably results from the renal haemodynamic effects of ACE inhibitors and predicts greater renal protective efficacy.[74] Thus, provided that the increase is <30% and is not progressive, an initial rise in serum creatinine should not be regarded as an indication for discontinuing ACE inhibitor or angiotensin receptor antagonist therapy. Patients with impaired renal perfusion are at increased risk of developing significant renal impairment. Therefore, it is important to ensure that CKD patients have adequate hydration, omit diuretics for 48–72 hours and avoid NSAIDs prior to starting an ACE inhibitor or angiotensin receptor antagonist. In addition, the ACE inhibitor or angiotensin receptor antagonist should be started at a low dose and titrated up. Serum creatinine and potassium levels should be checked 3–5 days after each dose increase.

Since both ACE inhibitor and angiotensin receptor antagonist treatment may cause a rise in serum creatinine or potassium in CKD patients, a greater incidence of these complications may be expected with combination therapy. However, the clinical studies described earlier found no difference in the incidence of such adverse events between combination and monotherapy. On the other hand, the CHARM-Added (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) study did report an increased incidence of drug discontinuation because of a rise in serum creatinine or hyperkalaemia in heart failure patients treated

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with combination ACE inhibitor and angiotensin receptor antagonist versus ACE inhibitor monotherapy.[75] We recommend that the same aforementioned precautions for initiating ACE inhibitor or angiotensin receptor antagonist be followed when combination therapy is started. The new drug should be started at the lowest available dose and increased with careful monitoring.

2.4 Dietary Protein Restriction

Dietary protein restriction was among the first interventions proposed to slow CKD progression. Unfortunately, clinical studies have failed to reproduce the clear benefit associated with low protein diet in experimental studies. Following the publication of several inconclusive studies the MDRD study was designed to provide an unequivocal answer. In this study, 585 patients with moderate chronic renal failure (CRF) [GFR 25–55 mL/min/1.73m^2] were randomised to a 'usual' (1.3 g/kg/day) or 'low' (0.58 g/kg/day) protein diet (study 1) and 255 patients with severe CRF (GFR 13–24 mL/min/1.73m^2) to a 'low' (0.58 g/kg/day) or 'very low' (0.28 g/kg/day) protein diet (study 2). Patients were also assigned to different levels of blood pressure control. The primary analysis after a mean follow-up of 2.2 years revealed no significant difference in the mean rate of GFR decline in study 1 or 2.[16] However, secondary analyses suggested that dietary protein restriction probably did afford some benefit. In study 1, an initial reduction in GFR, which probably resulted from functional effects of decreased protein intake, obscured a later reduction in the rate of GFR decline in the 'low' protein diet group.[16] Further analysis of data from study 1 also showed that dietary protein restriction achieved the greatest renal protective effect in those with the highest initial rates of decline in GFR.[76] In study 2, analysis of achieved protein intakes revealed that patients did not achieve the required protein restriction. When data from both diet groups were combined and analysed according to achieved dietary protein intake, a reduction in protein intake of 0.2 g/kg/day correlated with a 1.15 mL/min/year reduction in the rate of GFR decline, equivalent to a 29% reduction in mean rate of GFR decline.[77]

A meta-analyses of randomised studies provided further evidence supporting a renal protective effect of a low protein diet. Among 1413 patients with non-diabetic CKD from five studies, a low protein diet was associated with a relative risk of 0.67 for ESRD or death.[78] Similarly, among 108 patients with type 1 diabetes from five studies, a low protein diet significantly slowed the increase in albuminuria or the decline in GFR or creatinine clearance.[78] Whereas no single study has yet provided conclusive evidence for a renal protective effect of dietary protein restriction in humans, available evidence does support moderate protein restriction (0.6 g/kg/day) in patients with CKD and evidence of disease progression. It should be emphasised that the decision to institute dietary protein restriction should be individualised and it should be avoided in patients with low serum albumin levels because of nephrotic syndrome or malnutrition.

2.5 Treatment of Dyslipidaemia

CKD is commonly associated with dyslipidaemia characterised by elevated triglyceride-rich lipoproteins (very low-density and low-density lipoprotein) and reduced high-density lipoprotein levels.[79] In addition to contributing to the increased risk of cardiovascular disease among CKD patients, these lipid abnormalities may also accelerate the progression of CKD. Treatment of hyperlipidaemia in experimental studies has resulted in attenuation of renal injury in a variety of models of CKD.[80,81] Moreover, in one experimental study the renal protective effects of HMG-CoA reductase inhibitor (statin) treatment were additive to those of combination ACE inhibitor and angiotensin receptor antagonist therapy.[82] Whereas large randomised clinical trials of lipid-lowering therapy in CKD have not yet been published, a meta-analysis of 12 small studies found that lipid-lowering therapy significantly reduced the rate of decline in GFR (mean reduction 1.9 mL/min/year).[83] Furthermore, one study has shown that treatment of patients with non-diabetic CKD with maximum doses of an ACE

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inhibitor was associated with a reduction in hypertriglyceridaemia and hypercholesterolaemia. The effects on cholesterol appeared to be related to increases in serum albumin but changes in serum triglycerides did not correlate with changes in serum albumin.[84] These data, together with the increased cardiovascular risk in CKD, provide support for a policy of dietary and drug intervention to correct dyslipidaemia. Further studies are required to confirm the above findings in larger numbers of patients and to identify appropriate levels for intervention as well as therapeutic targets.

2.6 Smoking Cessation

Smoking is a risk factor for the development of microalbuminuria, overt proteinuria and renal disease progression in patients with type 1 and 2 diabetes.[85-87] Similarly, smoking has been associated with a greater risk of CKD progression in non-diabetic patients. It was the most powerful predictor of a rise in serum creatinine among patients with severe essential hypertension.[88] Patients with a primary glomerulonephritis and serum creatinine >1.7 mg/dL were significantly more likely to be smokers than those with normal creatinine levels.[89] Among patients with adult polycystic kidney disease or IgA nephropathy, smokers had a 10-fold increased risk of progression to ESRD compared with non-smokers.[90] Finally, the median time to ESRD was almost halved in smokers versus non-smokers among patients with lupus nephritis.[91] Proposed mechanisms whereby smoking may contribute to renal injury include glomerular hyperfiltration, endothelial dysfunction and increased albuminuria. Although no prospective studies showing renal benefit from smoking cessation have yet been published, the well established benefits of smoking cessation for prevention of lung and cardiovascular disease require that patients with CKD should be advised to stop smoking and assisted in achieving this goal.

2.7 Control of Hyperglycaemia

A detailed discussion of the role of glycaemic control in diabetic renal protection is beyond the scope of this article. In summary, there is strong evidence that tight glycaemic control significantly reduces the incidence of microalbuminuria and overt nephropathy among patients with type 1[92] and type 2[93] diabetes. In contrast, findings regarding the role of improved glycaemic control in those patients who already have microalbuminuria have been variable. Only two[94,95] of five small studies have shown a reduction in progression to overt nephropathy with tight versus normal glycaemic control among patients with type 1 diabetes with microalbuminuria.[94-98] On the other hand, evidence of histological reversal of diabetic glomerulopathy lesions in patients with type 1 diabetes with normo- or microalbuminuria following pancreatic transplantation suggests that tight glycaemic control is beneficial in this group.[99] Furthermore, the UK Prospective Diabetes Study did show a benefit of tight glycaemic control in delaying the development of overt proteinuria and slowing the rate of rise in serum creatinine in patients with type 2 diabetes with microalbuminuria.[100] No data are available to assess the renal protective effect of tight glycaemic control among diabetic patients with established nephropathy. On the basis of these data we recommend tight glycaemic control (target glycosylated haemoglobin <7%) in all diabetic patients for the

Table IV. Therapeutic interventions and goals for achieving optimal renal protection

1.	ACE inhibitor or angiotensin receptor antagonist as first-line therapy: consider combination therapy if goals not achieved with monotherapy
2.	Antihypertensive therapy: escalate to achieve a goal of <130/80mm Hg
3.	Minimise proteinuria: goal of <0.5 g/day
4.	Dietary protein restriction: 0.6 g/kg/day if appropriate
5.	Treat hyperlipidaemia
6.	Smoking cessation
7.	Tight glycaemic control in diabetic patients: glycosylated haemoglobin <7%

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prevention of microvascular complications including nephropathy. Despite the somewhat conflicting evidence, we also recommend continued tight glycaemic control in diabetic patients who develop microalbuminuria or overt nephropathy. However, decisions regarding glycaemic control should be individualised because the risks of severe hypoglycaemia may outweigh the benefits of tight glycaemic control in some patients.

3. Conclusion and Recommendations

Achieving optimal renal protection in clinical practice requires clear therapeutic goals and sustained effort. On the basis of available evidence we recommend seven simple goals as listed in table IV. ACE inhibitor or angiotensin receptor antagonist therapy should be regarded as fundamental to renal protective therapy, and combination therapy should be considered if blood pressure or proteinuria goals are not achieved with monotherapy. Many patients require multiple drugs and frequent visits to achieve the blood pressure target of <130/80mm Hg. Proteinuria should be monitored frequently and therapy should be escalated to minimise it. There are no prospective data to indicate the optimal level of proteinuria but a level of <0.5 g/day is generally regarded as optimal. It should be stressed that the interventions and treatments discussed and the tests required for monitoring are widely available and relatively inexpensive. Thus, achieving optimal renal protection should be regarded as a therapeutic goal for all patients with CKD. Recent efforts by the US NKF to raise the profile of CKD and renal protection issues illustrate the extent to which national organisations can assist in achieving renal protection for more patients (see the NKF website and NKF-Kidney Disease Outcomes Quality Initiative [K/DOQI] Clinical Practice Guidelines in particular[101]). Ongoing research continues to elucidate the complex mechanisms that contribute to CKD progression and it is hoped that new insights will lead to novel therapies to provide more effective renal protection. However, the challenge for the present is to extend the proven benefits of renal protection with currently available interventions to all patients.

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