

Retardation of Kidney Failure – Applying Principles to Practice

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Abstract

Over the next decade, the number of patients with end-stage renal disease (ESRD) treated by dialysis may double, and even developed nations will have difficulty in coping with this alarming increase. This review will outline the proven and unproven strategies that have the potential to retard the progression of chronic kidney disease (CKD). Recently, a number of randomised clinical trials have demonstrated the efficacy of several strategies to slow the progression of CKD. Proven strategies include adequate blood pressure control (with angiotensin blockade), and for diabetic nephropathy good glycaemic control. Other potentially beneficial strategies include smoking cessation, lipid control and aldosterone blockade. The early institution of these strategies has the potential to regress established CKD as well as improve the long-term cardiovascular outcomes of these patients. Proof of the efficacy in humans of promising experimental approaches, such as the administration of growth factors (e.g., recombinant bone morphogenetic protein-7), anti-fibrotic agents (e.g., pirfenidone) and novel anti-proteinuric drugs (e.g., pentosan polysulphate), is awaited. Finally, the primary prevention of CKD, at least in part, by the eradication of type 2 diabetes and obesity (through improvement of lifestyle factors), and adequate treatment of hypertension, have the potential to eliminate up to half of the most common causes of CKD (or ESRD) in developed countries.

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The Need

By 2010 there will be more than 2 million patients worldwide on maintenance dialysis, a 400% increase in 20 years.¹ This increase, occurring predominantly in developing nations, is being driven especially by a worldwide increase in the incidence of diabetes, and is too great to be offset by increased rates of renal transplantation. The societal and financial costs of renal replacement therapy are proving too great for developed nations to cope with, and are an impossible burden for developing nations to meet. The number of patients with end-stage renal disease (ESRD) is but the tip of the iceberg of the total number of patients with progressive chronic kidney disease (CKD). Over the past decade or so, there have been a number of relatively large hard-endpoint trials demonstrating the efficacy of several therapeutic strategies for slowing or even preventing the progression of CKD. These therapies may be effective in patients with even advanced disease yet

it appears that cardiovascular outcomes are better and total costs less if the treatments are instituted early in the course of disease. Universal application of these therapies has the potential to greatly reduce the burden of renal failure worldwide. In addition, there are a number of strategies of possible benefit whose efficacy remains to be proven. Proof of efficacy and widespread clinical application of these therapies was preceded and driven by basic research. There has been a rapid expansion of basic research into the pathogenesis of progressive CKD, which has exposed new targets for future therapies. The effectiveness of existing therapies means that much larger clinical trials will be required to prove the usefulness of any new strategies.²

This review will summarise the evidence for factors, proven and unproven, that cause progression of CKD, and the strategies proven or with potential to retard disease progression.

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Factors Causing Progression

Without treatment, renal function declines gradually in the majority of patients with CKD (Stages 2 to 4, US National Kidney Foundation Classification), eventually leading to kidney failure (Stage 5).^{3,4} However, the rate of progression shows considerable interindividual variability, and is dependent on multiple factors. The latter can be divided into at least 3 groups (Table 1): (i) *susceptibility factors* that increase vulnerability to develop chronic renal injury; (ii) *initiation factors* that directly cause renal damage; and (iii) *progression factors* that accelerate the deterioration in renal function following injury to the kidney.^{3,5}

Susceptibility factors cannot be specifically modified by current therapy, and are therefore defined as “non-modifiable”.⁶ Males have a two-fold higher rate of decline of chronic renal disease, possibly related to higher blood pressure as well as lack of oestrogen.⁶ The natural loss of glomerular filtration rate (GFR) of 1 mL/min/year from age 25, would suggest that the age at the time of CKD onset influences the amount of remaining viable kidney tissue (renal reserve).⁶ No new nephrons are formed post-partum, and recent studies suggest that nephron endowment at birth may have an important role in determining the rate of progression.⁷ The latter could link the higher incidence of ESRD in certain populations characterised by low birth-weight, such as indigenous Australians.⁸ Other, as yet, undetermined genetics factors may also mediate progression. Polymorphism of the angiotensin-converting enzyme is the most well studied (with some studies suggesting the DD phenotype associated with progression), and many other candidate genes are under investigation.⁹

The most important initiation factor, the cause of the underlying nephropathy, is an important determinant of rate of progression. Untreated diabetic nephropathy is considered to have the fastest rate of progression, with a typical rate of loss of GFR being 10 mL/min/year.¹⁰ The usual rate of progression of chronic glomerulonephritides is estimated to be 2.5 and 1.5 times faster than chronic tubulointerstitial diseases and hypertensive nephrosclerosis respectively.¹¹

Table 1. Factors that Mediate Progression

Susceptibility factors
Male gender, increasing age, genetic and racial background, reduced nephron number at birth
Initiation factors
Primary aetiology of chronic kidney disease
Progression factors
Hypertension, nephrotic-range proteinuria, hyperglycaemia, hyperlipidaemia, smoking, pregnancy, nephrotoxins, presence of glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis on the renal biopsy

Sustained elevation in the systemic blood pressure (greater than 140/90 mm Hg) and nephrotic-range proteinuria are the most important *progression factors* that strongly predict renal function decline, regardless of the underlying cause of CKD.¹² In addition, it is well established that the severity of tubular atrophy and interstitial fibrosis on the renal biopsy predicts a poor renal outcome.¹³ Although some studies suggest that the latter is the best histological marker of progression, accurate stereological and serial sectioning techniques reveal that glomerulosclerosis is also an important histological predictor of poor outcome.¹⁴ Studies suggest that factors such as hyperglycaemia,¹⁵ hyperlipidaemia,¹⁶ smoking¹⁷ and pregnancy¹⁸ (in the presence of impaired GFR) also predict a more rapid progression. Other factors for which there is some evidence (but not proven in humans) include obesity,^{19,20} hyperuricaemia,²¹ increased sympathetic nervous system activity,²² hyperphosphataemia,²³ acidosis,²⁴ and endogenous cortisol synthesis.²⁵

Experimental Insights

The pathophysiological basis of CKD progression is the permanent loss of functioning nephrons, which leads to compensatory changes in the remaining nephrons that, over time, become maladaptative.²⁶⁻³⁰ The latter paradoxically causes further tissue injury and nephron loss, and disease progression, independent of the primary cause of the renal disease.²⁶⁻³⁰ Experimental studies, performed predominantly in laboratory rats, have revealed some of the mechanisms and potential molecular mediators that may be involved in this process. These can be understood in terms of the 3 common pathological endpoints of CKD (present irrespective of the primary cause): (i) glomerulosclerosis; (ii) tubulointerstitial damage; and (iii) vascular sclerosis.

Glomerulosclerosis is defined as the accumulation of extracellular amorphous material and matrix with obliteration of structural elements of the glomerulus. Brenner and other workers found that a reduction in nephron number due to chronic renal injury leads to glomerular capillary hypertension in the remnant nephrons.²⁶⁻³⁰ Hydrostatic forces cause damage to the glomerular endothelium,³¹ leading to a chain of events that include glomerular hypertrophy,²⁸ macrophage accumulation in the mesangium,³² mesangial cell proliferation/dedifferentiation,³³ stretching of podocytes, podocyte dysfunction and loss;^{29,34} and/or apoptosis of mesangial and endothelial cells.³⁵ The end result is the loss of cellular elements in the glomerulus, matrix deposition and expansion, formation of tuft adhesions, misdirected glomerular filtrate (leading to atubular glomeruli)³⁶ and proteinuria.³⁰ Recently, podocyte dysfunction and loss has been postulated to play a critical role in this process, given their role in maintaining the glomerular filtration barrier

(preventing the passage of plasma proteins into the tubular lumen) and their inability to regenerate/replicate following injury.^{29,34}

Tubulointerstitial damage (tubular atrophy, interstitial inflammation and fibrosis) is a common feature of all types of CKD, irrespective of the primary cause.³⁷ Chronic injury to tubular epithelial cells is probably the initial event that leads to tubulointerstitial damage.³⁷ Injury to tubular epithelial cells may be caused by the cytotoxic effects of filtered plasma proteins (lipids, albumin and albumin-bound moieties, immunoglobulins and complement);^{30,37} cytokines and inflammatory mediators present in the tubular lumen or released by tubular and infiltrating inflammatory cells;³⁷ adaptive hypermetabolism of remaining nephrons³⁸ and oxidative stress; and relative or absolute tubulointerstitial hypoxia.³⁹ Injured tubular cells release a variety of proinflammatory, chemotactic and profibrotic factors that lead to accumulation of an interstitial mononuclear cell infiltrate, interstitial fibrosis, tubular atrophy and apoptosis, and tubular cell-myofibroblast transition.⁴⁰

Hyalinosis and sclerosis of peritubular capillaries have been demonstrated in humans and experimental models of CKD.⁴¹ In experimental models, loss of peritubular capillaries may be mediated by a reduction in angiogenic peptides such as vascular endothelial growth factor.⁴¹ Both of these processes could exacerbate tubulointerstitial fibrosis by inducing hypoxia.

A variety of molecular mediators produced by resident renal (mesangial, tubular epithelial), infiltrating inflammatory (macrophages) and mesenchymal cells (fibroblasts) have been shown to be involved in the development of these pathological endpoints.^{42,43} These include growth factors, chemokines/cytokines, eicosanoids,

vasoactive peptides (such as angiotensin, aldosterone, endothelin), inflammatory mediators, and components of coagulation and matrix turnover systems. Of these, that excessive production of angiotensin II promotes renal disease progression is the best supported hypothesis.³⁰

Slowing or Reversing Progression

Proven Strategies

Strategies which have been proven in randomised controlled trials to slow the progression of diabetic and non-diabetic CKD are summarised in Table 2. Evidence and guidelines for implementing these strategies are discussed in more detail on the CARI Website.⁵

Blood pressure control. The single most important means of slowing disease progression is adequate control of systemic blood pressure. The greater anti-proteinuric effect of a low blood pressure target has been proven in large trials^{4,44,45} and was shown in a recent meta-analysis of 11 trials to be associated with reduced progression.⁴⁶ The need for a low-normal blood pressure applies particularly to proteinuric patients^{46,47} and those with diabetes. The evidence has been gleaned from trials involving angiotensin-converting enzyme (ACE) inhibitors but probably applies to other antihypertensive therapies as well. As a result of this evidence, the current guidelines are for a blood pressure <130/80⁵ and a systolic as low as 110⁴⁶ in proteinuric patients, if tolerated. It should be remembered that the goals of anti-hypertensive treatment in CKD are not only to lower blood pressure and slow disease progression, but also to reduce the risk of cardiovascular disease.

ACE inhibitors. ACE inhibitors have been shown to slow the progression of diabetic⁴⁸ and non-diabetic renal disease^{47,49} in comparison to placebo, and in comparison to

Table 2. Strategies of Proven Efficacy for Retarding Progression of Chronic Kidney Disease

Strategy	Evidence	Comment
Tight BP control	MDRD, ⁴ ABCD, ⁴⁴ AASK, ⁴⁵ AIPRD ⁴⁶	Target blood pressure: 110-130/75-80, if tolerated
ACE Inhibitor	Lewis, ⁴⁸ APRI ⁴⁹ REIN, ⁸ AASK ⁴⁵	Target proteinuria <500 mg/d
ARB	RENAAL, ⁵² IDNT ⁵³	First choice if ACE inhibitor-intolerant
ACE Inhibitor + ARB	CALM, ⁵⁷ COOPERATE ⁵⁸	Greater anti-hypertensive and anti-proteinuric effect with reduced progression
Dietary protein restriction	MDRD, ⁴ Kasiske ⁵⁹	
Blood sugar control	DCCT (type 1 DM), ¹⁵ UKPDS (type 2 DM) ⁶⁰	

AASK: African American Study of Kidney Disease and Hypertension; ABCD: Appropriate Blood Pressure Control in Diabetes; ACE: angiotensin-converting enzyme; AIPRD: ACE Inhibition in Progressive Renal Disease; APRI: Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency Study Group; ARB: angiotensin receptor blocker; BP: blood pressure; CALM: Candesartan and Lisinopril Microalbuminuria; COOPERATE: combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease; DCCT: Diabetes Control and Complications Trial; IDNT: Irbesartan Diabetic Nephropathy Trial; MDRD: Modification of Diet in Renal Disease; RENAAAL: reduction in endpoints in NIDDM with angiotensin II antagonist losartan; REIN: Ramipril Efficacy in Nephrology; UKPDS: UK Prospective Diabetes Study

a non-dihydropyridine channel blocker.⁴⁵ The protective action of ACE inhibitors is probably a class effect, and can be seen even with relatively low doses. However, as higher doses have a greater anti-proteinuric effect (even in the absence of a greater reduction in blood pressure), the maximum tolerated dose should be used. The protective effect of ACE inhibitors correlates with the initial level of proteinuria,⁴⁸ and is seen even in patients with low-grade proteinuria,⁴⁷ or advanced renal disease.⁵⁰ In patients who have achieved target blood pressure, therapy can be further titrated to achieve a target protein excretion of less than 500 mg/day. The anti-hypertensive effect of ACE inhibitors can be significantly improved by the addition of a diuretic or salt restriction.⁵¹ The risk of disease progression was reduced by up to 50% in some of these trials and progression may even be halted completely.⁴⁷ The cardio-protective effect of ACE inhibitors appears to be greater for high-risk patients, such as diabetics with renal insufficiency, than low-risk patients such as those with normal blood pressure, and normal renal function.

Angiotensin receptor antagonists. Angiotensin receptor antagonists (ARBs) have been shown to slow progression in patients with type 2 diabetes.^{52,53} The relative risk of ESRD was reduced by 20% to 30% in these studies. Interestingly, the protective effect of the ARB losartan was shown by post-hoc analysis of the RENAAL study⁵² to be confined to Asian patients. This is perhaps not too surprising considering the proven marked racial differences in rates of disease progression. In type 2 diabetic patients with microalbuminuria, the ARB irbesartan was shown to reduce the progression to clinical diabetic nephropathy.⁵⁴ ARBs are the first-line therapy for ACE inhibitor-intolerant patients, but probably not in others until they have shown to be as cardio-protective as ACE inhibitors.^{55,56}

Combined ACE inhibitor and ARB. A combination of an ACE inhibitor and ARB has been shown in several trials to have a greater anti-proteinuric effect than either treatment alone,^{57,58} and recently has been shown to have a greater effect on slowing the progression of renal disease.⁵⁸ However, it remains uncertain whether combination therapy in non-maximal doses is really more efficacious than either drug in maximal doses. As with ACE inhibitor and ARB therapy alone, the addition of diuretic and/or salt restriction will increase the anti-hypertensive and anti-proteinuric effect of combination therapy.

Dietary protein restriction. Restriction of dietary intake is anti-proteinuric and may reduce disease progression in diabetic and non-diabetic renal disease,⁵⁹ but the clinical effect is probably small⁴ and therefore Australian recommendations are to avoid malnutrition by following a normal protein diet of 0.5 to 1.0 g/kg/day.⁵

Blood sugar control. In type 1 diabetes, intensive glucose

control has been shown to reduce the development and progression of albuminuria, a surrogate for disease progression.¹⁵ In type 2 diabetics, intensive glycaemic control produced better microvascular outcome with slowed progression.⁶⁰

Unproven Therapies

There are many other therapies that have been proposed to slow the progression of CKD. With some, evidence is based on surrogate markers such as proteinuria, or comes from small trials. The CARI web site provides a useful and detailed summary of the evidence.⁵ As proteinuria is a hallmark of, and pathogenetic factor for, disease progression, it is likely that anti-proteinuric therapies may also slow progression to ESRD. Other anti-proteinuric therapies with this potential are summarised in Table 3 and discussed in more detail in reference 51.

Calcium entry blockers. Dihydropyridine calcium entry blockers (CEBs) do not reduce proteinuria^{44,45,53} despite lowering blood pressure, and may hasten disease progression in comparison with ACE inhibitors and beta blockers.⁴⁵ In contrast, non-dihydropyridine CEBs are anti-proteinuric, and therefore have the potential to retard progression. Dihydropyridine CEBs may be used in patients with renal disease when combined with anti-proteinuric drugs such as ACE inhibitors and ARBs.

Table 3. Other Anti-proteinuric Therapies Which May Retard the Progression of Chronic Kidney Disease in Humans

Strategy	Evidence	Comment
Avoid DHCEB	ABCD, ⁴⁴ AASK, ⁴⁵ IDNT ⁵³	DHCEB not anti-proteinuric
β-blocker	AASK ⁴⁵	NDH CEB anti-proteinuric
Restrict NaCl		Increase anti-hypertensive and therefore anti-proteinuric effects of ACE inhibitors and ARBs.
Control fluids	MDRD ⁴	
Aldosterone antagonist	Sato ⁶¹	Especially in type 2 DM with aldosterone escape on ACE inhibitor
Lipid control	Fried ¹⁶	Particularly HMG CoA reductase inhibitors
Cease smoking	Orth ¹⁷	

AASK: African American Study of Kidney Disease and Hypertension; ABCD: Appropriate Blood Pressure Control in Diabetes; ACE: angiotensin-converting enzyme; DHCEB: dihydropyridine; DM: diabetes mellitus; HMG CoA: 3-hydroxy-3-methylglutaryl coenzyme A; MDRD: Modification of Diet in Renal Disease; NDH CEB: non-dihydropyridine calcium entry blocker

Table 4. Experimental Approaches to Retard Renal Failure Progression

Exogenous recombinant growth factor proteins (e.g., HGF, BMP-7, VEGF)
Anti-fibrotic drugs and recombinant proteins (e.g., relaxin, pirfenidone)
Anti-inflammatory drugs (e.g., immunosuppressants)
Cytokine and chemokine antagonists and modulators
Endothelin receptor antagonists
Aldosterone antagonists
Retinoids and vitamin D
Anti-proteinuric agents (e.g., pentosan polysulfate, neutralising antibody against heparanase, C5b-9)
Modulators of cell cycle regulatory proteins
Modulators of intracellular signaling pathways (e.g., protein kinase C inhibitor, ruboxistaurin; MAPK)

BMP-7: bone morphogenetic protein-7; HGF: hepatocyte growth factor;
MAPK: mitogen activated protein kinase; VEGF: vascular endothelial
growth factor

Beta blockers. Beta blockers may have as great an anti-proteinuric effect as ACE inhibitors.⁴⁵ Some of their probable ability to slow disease progression may involve a sympatholytic action. In fact, ACE inhibitors and ARBs are also sympathicoplegic.

Aldosterone antagonists. Patients on ACE inhibitors who develop “aldosterone escape” may also escape from their anti-proteinuric effect⁶¹ and the addition of spironolactone (25 mg/day) to type 2 diabetics with aldosterone escape has recently been shown to reduce urinary albumin excretion.⁶¹ As patients with diabetes mellitus have been shown to have increased plasma renin activity and angiotensin and aldosterone concentration, it remains to be determined whether this effect is more prominent in or unique to diabetic patients.

Lipid control. The potential of anti-lipemic therapy, in particular HMG CoA reductase inhibitors, to retard progression remains unproven, and derives from trials with small numbers and generally short follow-up times.¹⁶ The added benefit of anti-lipemic therapy, of course, is its beneficial effect on vascular disease, which is so prevalent in patients with CKD.

Smoking. Epidemiological studies show that cigarette smoking is associated with proteinuria and disease progression.¹⁷ Given the marked effects of smoking on cardiovascular risk, there is no doubt that renal patients should be strongly advised to cease.

There are a number of other treatments, including control of uric acid, phosphate restriction, exercise and erythropoietin^{5,51} for which there is circumstantial, anecdotal or inconsistent evidence favouring their efficacy. Whether or not they should be applied universally or in particular patient sub-groups to slow disease progression, will need to

wait the outcome of adequately designed studies.

Experimental Possibilities

Recent studies suggest that the early institution of existing therapies, such as angiotensin blockade, has the potential to reverse established scarring in experimental models of CKD.⁶² In addition, future therapeutic approaches include more specific measures to reduce proteinuria, interstitial inflammation/fibrosis, tubular atrophy and glomerulosclerosis. As a result of intense basic science research activity, the next decade may see the clinical application of some of these therapeutic approaches, synergistically with existing therapy.

Recently, rapid progress has been made in understanding the molecular structure of the glomerular filtration barrier, and it is expected that this will lead to new and more specific therapies to reduce proteinuria.⁶³ Other potential experimental approaches to reduce proteinuria include pharmacological agents that modify glomerular basement membrane turnover (such as pentosane polysulphate⁶⁴ or heparanase⁶⁵) and block inflammatory mediators which increase glomerular permeability (such as complement C5b-9⁶⁶). Methods to prevent protein-mediated tubulointerstitial injury might include agents that block receptors (megalin and cubulin) which mediate protein uptake into proximal tubular cells⁶⁷ or drugs that neutralise the cytotoxic effects of filtered plasma proteins (e.g., complement C5b-9) on tubular cells.⁶⁸

Experimental approaches to reactivate signal transduction pathways that were induced at the time of embryonic kidney development may help regenerate a chronically injured kidney. Bone morphogenetic protein (BMP)-7, a member of the TGF- β superfamily, is highly conserved and has an important role in the formation of the developing kidney.⁶⁹ Interestingly, the administration of recombinant BMP-7 prevented tubular atrophy, interstitial inflammation and fibrosis in rats with unilateral ureteric obstruction (a good model of chronic tubulointerstitial fibrosis).⁶⁹ Similarly, chronic BMP-7 administration reduced tubulointerstitial fibrosis and glomerulosclerosis in the MRL *lpr/lpr* mouse model of lupus nephritis,⁷⁰ and reduced renal hypertrophy and proteinuria in rats with streptozotocin-induced diabetes.⁶⁹ Significantly, BMP-7 was more effective than angiotensin-converting enzyme inhibition in these studies.⁶⁹ There is also evidence that BMP-7 reduces vascular calcification and this could have further benefits in CKD.⁶⁹

Other molecular targets for intervention include growth factors [transforming growth factor- β 1, hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), connective tissue growth factor, fibroblast growth factor],⁴⁰⁻⁴² cytokines (interleukins and TNF), chemokines (MCP-1 and others),⁴³ cell cycle regulatory proteins,⁷¹

inflammatory mediators (such as complement), endothelin,⁷² aldosterone,⁶¹ anti-fibrotic molecules (relaxin),⁷³ components of intracellular signalling pathways (such as ruboxistaurin, a protein kinase C inhibitor; or mitogen-activated protein kinase system)^{74,75} and antioxidants. Of these, the exogenous administration of recombinant HGF and VEGF show promise, as do endothelin receptor antagonists. A number of other agents are also under investigation in clinical trials, including pirfenidone (an anti-fibrotic drug for the treatment of focal segmental glomerulosclerosis)⁷⁶ and a humanised antibody against complement C5b-9 (for the treatment of membranous nephropathy).⁶⁶ The results of these studies in humans are awaited with interest.

Uncertainty remains about which of these molecular mediator/s should be targeted, and at what point in the disease process, and how their renal expression should be modified *in vivo* in a cell-specific manner. In addition, methods of altering gene expression also require investigation and include humanised antibodies, chimeric soluble receptors, vaccination, aptamers, siRNAs, antisense oligodeoxynucleotides, decoy DNA, DNA enzymes and gene therapy.^{42,77} Testing these inhibitors in clinical trials will be problematic, for reasons raised earlier. Moreover, the cost-effectiveness of these new agents will require proof and may limit their clinical application. Despite these problems, there is no doubt that the next few decades will yield important advances in the treatment of CKD progression.

Summary

The incidence and prevalence of ESRD is increasing at an alarming rate, and it is unlikely that the economic resources and infrastructures of even developed nations will be able to meet this demand over the next two decades. This is a crisis that cannot be prevented, but could be reduced. At this point in time, the early identification, referral and treatment of patients with CKD is the primary way to slow the future growth of ESRD. Strategies proven to retard the progression of CKD must be instituted early in order to improve cardiovascular outcomes and potentially stabilise and retard renal disease progression. Funding for such strategies should also be made available to developing nations. Clinical trials of new experimental approaches, such as BMP-7, will hopefully prove their efficacy in humans, and expand the future options for the management of CKD progression. Finally, prevention of CKD, at least in part, by the eradication of type 2 diabetes and obesity (through improvement of lifestyle factors), and adequate treatment of hypertension, has the potential to eliminate at least a third of the common causes of ESRD in developed countries.²⁰

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