The progression of chronic renal failure (CRF) levels. In the MRFIT study, the risk of developing ESRD increased exponentially with increasing levels of blood pressure. Patients with underlying chronic renal disease are also at increased risk from hypertensive-induced renal damage. This is likely to be due to the susceptibility of their glomeruli to systemic hypertension, as remnant glomeruli are poorly auto-regulated and therefore allow the unopposed transmission of systemic hypertension to their capillary bed. The ensuing glomerular capillary hypertension accelerates the development of glomerulosclerosis.

Having established that systemic hypertension accelerates the progression of CRF, experimental and clinical evidence has confirmed the beneficial effect of its control on the progression of diabetic and nondiabetic nephropathies. However, questions have been asked as to target blood pressure and the type of antihypertensive agents used. Before we examine the arguments for different target blood pressures and preferential use of some antihypertensive agents, we shall examine briefly the role of other risk factors affecting the progression of CRF that may interact with hypertension and influence its management.

It has been known for many years that proteinuria is a good predictor of progressive CRF. The North Italian Cooperative Study Group has recently confirmed the importance of proteinuria as a poor prognostic factor in patients with CRF. In this study, the rate of decline of renal function was proportional to the severity of proteinuria, with patients with heavy proteinuria (＞3 g/24 h) having the worst prognosis. Recently, an increasing body of experimental data has suggested that proteinuria may be nephrotoxic, thus contributing to the progression of renal disease.

The progression of chronic renal failure (CRF) remains one of the main challenges in clinical nephrology. Over the last quarter of a century, animal experimentation has identified many of the pathological mechanisms underlying the associated renal scarring process. Consequently, research has implicated a wide range of mediators, including prominent roles for cytokines, chemokines and growth factors. This has suggested therapies based on the manipulation of these mediators and aimed at the prevention of progressive renal fibrosis and functional decline. Unfortunately, the relevance of these interventions and their applicability to patients with progressive renal insufficiency remain uncertain. Meanwhile, nephrologists continue to be faced with an increasing number of patients with progressive CRF. It is therefore imperative to review available clinical interventions based on the manipulation of known clinical risk factors for the progression of CRF.

Hypertension has been linked to the progression of chronic renal failure (CRF) since the pioneering days of Richard Bright in the 19th century and Volhard and Farr early this century. More recently, a large body of evidence has suggested that the progression of CRF is accelerated by raised systemic blood pressure. The Multiple Risk Factor Intervention Trial (MRFIT) identified systemic hypertension as a significant risk factor for the development of endstage renal disease (ESRD). This study also confirmed the increased susceptibility of hypertensive Black patients to progressive renal failure. The Modification of Diet in Renal Disease (MDRD) study showed that the progression of CRF was linked to the level of systemic blood pressure with Black as well as proteinuric patients both at increased risk. More recently, the North Italian Cooperative Study Group identified a mean arterial blood pressure (MAP) value of 107 mmHg (around 140/90 mmHg) as discriminatory, with patients with higher values having an accelerated loss of renal function over a 30-month follow-up period. Others have identified a diastolic blood pressure value of 85–90 mmHg, with patients with higher values having a rate of progression almost twice as fast as those with lower blood pressure levels. In the MRFIT study, the risk of developing ESRD increased exponentially with increasing levels of blood pressure. Patients with underlying chronic renal disease are also at increased risk from hypertensive-induced renal damage. This is likely to be due to the susceptibility of their glomeruli to systemic hypertension, as remnant glomeruli are poorly auto-regulated and therefore allow the unopposed transmission of systemic hypertension to their capillary bed. The ensuing glomerular capillary hypertension accelerates the development of glomerulosclerosis.

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The transudation of protein and proteinaceous material through glomeruli with a raised capillary pressure is likely to cause glomerular cells to proliferate and increase their synthesis of extracellular matrix (ECM) components. Similarly, the increased filtration of proteins and their reabsorption by proximal tubular cells has been shown to stimulate the proliferation of these cells, and their release of chemokines and cytokines as well as their synthesis of ECM. With that in mind, proteinuria is becoming to be seen...
as an important consequence of systemic and glomerular hypertension that may be contributing directly to both glomerulosclerosis and tubulointerstitial fibrosis. The reduction of proteinuria should therefore be an important goal of antihypertensive therapy. It is also a good predictor of the long-term success of antihypertensive treatment of progressive CRF.  

Hyperlipidaemia has been linked to the progression of CRF for many years. Experimental evidence has confirmed an association, as exposure of glomerular and tubular cells to low-density lipoprotein (LDL) and its oxidized variant (oxLDL) stimulates their proliferation, induce injury and apoptosis, and stimulates their ECM production, thus contributing to fibrosis. 

The reduction of hyperlipidaemia through dietary or pharmacological manipulations prevents progressive experimental CRF. In patients with CRF, an association has been described linking serum cholesterol and triglycerides levels and the progression of diabetic and non-diabetic nephropathies. More specifically, raised circulating levels of LDL and apoprotein B correlate closely with the rate of decline of CRF, particularly the levels of complex triglyceride-rich Apo-B containing lipoproteins. Of interest, an additive detrimental effect on renal function of hyperlipidaemia and proteinuria was described in patients with CRF. Clinical data showing that the reduction of hyperlipidaemia slows the progression of CRF are lacking, although anecdotal reports suggest that correction of hyperlipidaemia is associated with a reduction in proteinuria. 3-hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors may have additional renoprotective effects, as these agents have been shown to inhibit mesangial proliferation and ECM production. 

Antihypertensive strategies may have in the future to be lipid-friendly, avoiding worsening of hyperlipidaemia and preferably reducing circulating lipids levels. 

Over the last decades, more attention has been paid to the potential nephrotoxicity of cigarette smoking. The Multiple Risk Factor Intervention Trial (MRFIT) has identified smoking as an independent risk factor for the development of end-stage renal disease (ESRD). Smoking can exacerbate systemic hypertension. Smoking as little as a single cigarette is associated with a rise in systemic blood pressure. In essential hypertension, the prevalence of microalbuminuria is almost double in smokers, while in diabetic patients the risk of microalbuminuria is 2.8 greater in smokers. In insulin-dependent diabetes mellitus (IDDM) patients, smoking also accelerates the progression from microalbuminuria to overt proteinuria. Tobacco smoking has been shown to have direct renal haemodynamic effects leading to glomerular hyperfiltration which may explain the detrimental effect of smoking on proteinuria. Others have suggested that smoking could reduce renal perfusion through an endothelin-mediated vasoconstriction. Smoking is also known to worsen hyperlipidaemia. These observations may explain the recent finding that cigarette consumption affects the rate of decline of CRF in a dose-dependent fashion, with the risk of ESRD in those smoking in excess of 15 packs-year increased 5.8-fold. Of interest, in this study the odds ratio for ESRD in smokers was even higher in those not treated with an angiotensin-converting-enzyme inhibitor (ACEI), reaching 10.1-fold compared to those treated with an ACEI, who had an odds ratio of 1.4. With these observations in mind, antihypertensive strategies should include a reduction or stoppage of smoking. 

The first question I would like to address is what should be the target blood pressure to slow or halt the progression of CRF? Data from the MRFIT and the MDRD have identified African-Americans and proteinuric patients at increased hypertensive risk. This led to the suggestion that these patients should achieve lower blood pressure levels in order to reach a similar level of protection against progressive CRF. While a normalization of blood pressure (mean arterial pressure [MAP] of 107 mmHg [140/90 mmHg]) may be sufficient to slow the progression of White patients with no proteinuria, lower levels (MAP <98 mmHg [130/80 mmHg]) should be aimed for in Black patients, and those with minimal proteinuria (1 g/24 h). By contrast, more aggressive antihypertensive control (MAP <92 mmHg [120/70 mmHg]) should be aimed for in patients with heavy proteinuria (>3 g/24 h) in order to achieve the same level of renal-function protection. In diabetic patients, preliminary data suggest that the level of blood pressure control may also be a function of the quality of glycaemia control; patients with poor glycaemia control (glycosylated haemoglobin levels/ HbA1c > 9.2%) having a faster rate of decline of renal function compared to those with a better metabolic control for an equal degree of blood pressure control. With good metabolic control (HbA1c < 9.2%), MAP of approximately 95 mmHg led to the normalization of the rate of decline in glomerular filtration rate (1–1.5 ml/min/year). In these type 1 diabetic patients, the effect of blood pressure and metabolic control on progression was independent of the type of antihypertensive agent used (ACEI or non-ACEI). These observations highlight the interdependence of risk factors in the control of progressive CRF. Whether other metabolic risk factors, such as hyperlipidaemia, have also to be taken into consideration in relation to blood pressure control is currently unknown. 

The second question centres around the type of antihypertensive agent used. A large and growing body of evidence favours ACE inhibitors. They control systemic as well as glomerular hypertension and reduce proteinuria; in other words, the perfect profile
for slowing the progression of CRF. Large clinical trials in diabetic\textsuperscript{39} and non-diabetic\textsuperscript{31,32} nephropathies seem to confirm this impression. As mentioned above, these agents may also have a therapeutic advantage in hypertensive smokers. On the other hand, they may be less effective when compared to other agents in Black patients. In diabetic and non-diabetic progressive nephropathies, ACEIs may prove more effective than other drugs in heavy proteinuric patients (\(> 5 \text{ g}/24 \text{ h}\)) and at higher levels of blood pressure control (MAP between 100 and 102 mmHg).\textsuperscript{9} If lower levels of blood pressure control (MAP around 92 mmHg) are reached through other antihypertensive agents, the beneficial advantage of ACE inhibitors may be reduced.\textsuperscript{8} Emerging data in NIDDM suggest that non-dihydropyridine calcium channel blockers (NDCCB) such as diltiazem\textsuperscript{33} and verapamil\textsuperscript{34} are equally effective in reducing overt proteinuria. Diltiazem, unlike nifedipine, seems to have a similar effect on glomerular size permselectivity to ACE inhibitors.\textsuperscript{35} Diltiazem also appears to be as effective as the ACE inhibitor lisinopril in slowing the progression of diabetic nephropathy in patients with type II diabetes.\textsuperscript{33} The combination of an ACE inhibitor (trandolapril) and a NDCCB (verapamil) appears to be additive in proteinuric patients with NIDDM.\textsuperscript{34} The United Kingdom Prospective Diabetes Study (UKPDS) implied that as long as a tighter blood pressure control is achieved (144/72 mmHg vs. 154/84 mmHg) in NIDDM patients with microvascular disease, it did not matter whether they were treated with captopril or atenolol.\textsuperscript{36} In non-diabetic nephropathies, the therapeutic advantage of ACE inhibitors is associated with better blood pressure control.\textsuperscript{31,32} A meta-analysis of the use of ACE inhibitors in non-diabetic nephropathies could not dissociate their protective effect from their antihypertensive efficacy.\textsuperscript{37} One prospective European study failed to show a different outcome in patients with progressive CRF treated with nifedipine or captopril for a 3-year period when the target blood pressure was <102 mmHg.\textsuperscript{38} Antihypertensive therapy in CRF should be tailored to the patient. Those at increased risk of hypertensive and/or diabetic damage (patients of African or Asian descent and those who are proteinuric) should have tighter blood pressure control, with lower levels when compared to others. In such patients, we should be aiming for MAP levels around 90–92 mmHg (120/70 mmHg) and a reduction of proteinuria (\(< 1 \text{ g}/24 \text{ h}\)). If this is easier to achieve with an ACE inhibitor, then they should be preferentially used. However, caution should be used against the indiscriminate use of these agents, as they could, in susceptible patients, accelerate the decline of renal function. Dietary salt restriction should be recommended in view of the salt sensitivity of patients with CRF, and the beneficial effect of such restriction on blood pressure control.\textsuperscript{40} Patients should stop smoking, as this is likely to reduce proteinuria, facilitate blood pressure control and ultimately slow progression. Lipids should be monitored, in particular LDL and apoprotein B levels and corrected with an HMG-CoA reductase inhibitor in view of the presence of associated hypertension and renal disease. We should avoid antihypertensive agents that may exacerbate hyperlipidaemia. All antihypertensive agents are not created equal and neither are the patients who suffer from CRF.

A.M. El-Nahas
Sheffield Kidney Institute
Northern General Hospital
N. Tamimi
Renal Unit
Kent and Canterbury Hospital

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