

## Progression of Renal Failure – The Role of Hypertension

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### Abstract

High blood pressure plays a key role in the progression of renal failure. Hypertension is a common presentation of kidney disease and an almost invariable accompaniment of renal failure. Hypertension is also a major contributor to cardiovascular disease, the major cause of morbidity and mortality in renal failure. Hypertension is both cause and consequence of renal failure, but the precise nature and prevalence of hypertensive nephrosclerosis as a cause of renal failure remains controversial. There is strong evidence that hypertension accelerates the progression of experimental renal disease and that control of blood pressure is effective in preventing this progression. Hypertension, both accelerated and “benign” (a misnomer), has long been recognised as a poor prognostic feature in human renal disease and more recently in renal allograft survival. Blood pressure control is very effective in retarding renal disease progression. There are compelling indications for angiotensin-converting enzyme inhibitors in both non-diabetic and type 1 diabetic nephropathies, and for angiotensin receptor blockers in type 2 diabetic nephropathy. Most patients will require combination drug therapy to control blood pressure and reduce both progression of renal failure and the associated cardiovascular morbidity and mortality.

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**Key words:** Angiotensin receptor blockers, Converting enzyme inhibition, High blood pressure, Proteinuria, Renal protection

### Introduction

Hypertension, or perhaps more accurately high blood pressure, plays a pivotal role in the progression of renal failure. The dichotomy of “hypertension” and “normotension” fails to recognise that the risks of adverse cardiovascular and renal events are directly related to increasing levels of blood pressure, even within the “normotensive” range and that blood pressure lowering may benefit high-risk patients (particularly those with renal disease) who are not “hypertensive” by conventional definition.<sup>1</sup> “Increasingly the very terms hypertension, hyperglycaemia and hypercholesterolaemia will probably disappear, as the focus moves from treating a theoretically decided cut-off point towards managing continuous distributions of risk ...”.<sup>2</sup>

With that caveat, this article will consider (1) the prevalence of hypertension in renal disease and renal failure, (2) the role of hypertension as a determinant of cardiovascular morbidity and mortality in renal failure, (3) hypertension as both cause and consequence of renal

disease, (4) hypertension in the progression of experimental renal disease, (5) hypertension in the progression of human renal failure and renal disease and (6) the options for treatment.

### 1. Prevalence of Hypertension in Renal Disease

Richard Bright was the first to recognise the association between hypertension and renal disease. He noted, “The hypertrophy of the heart seems in some degree to have kept pace with the advance of the disease in the kidneys”.<sup>3</sup> This was initially documented by Volhard and Fahr.<sup>4</sup>

Hypertension is a common presentation of kidney disease and mandates careful urine examination, including microscopy. Virtually all forms of renal disease can cause hypertension, particularly in the presence of renal impairment, although hypertension is more frequent in vasculitis and glomerulonephritis than in interstitial disease.<sup>5,6</sup> Primary renal disease leads to some 3% to 4% of hypertension in population studies and renovascular disease to around 1%. Hypertension is the rule in patients with end-

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stage renal failure (ESRF), some 80% to 90% of whom are hypertensive when presenting for dialysis. Globally, diabetic nephropathy has overtaken glomerulonephritis as the leading cause of end-stage disease. The prevalence of hypertensive nephropathy as a cause of ESRF depends on the population studied and the extent to which investigation for underlying causes is pursued.

## 2. Hypertension and Cardiovascular Morbidity/Mortality in Renal Failure

Renal disease, particularly diabetic nephropathy, is a predictor of major cardiovascular disease (CVD) events.<sup>7</sup> In Australia, more than half the patients with ESRF die from a cardiac or vascular event,<sup>8</sup> and identification and treatment of hypertension and other cardiovascular risk factors is imperative. In Western countries, cardiac mortality for dialysis patients is 10- to 20-fold that of the general population.<sup>9</sup> Similarly, the presence of proteinuria is associated with a markedly increased risk of CVD in hypertensives,<sup>10</sup> and also in those with high CVD risk.<sup>11</sup>

Smoking is also important in this context. Not only is it a powerful risk factor for CVD, but it accelerates progression of renal disease and is thus one of the most important remediable risk factors.<sup>12</sup> Obesity is another independent risk factor for CVD, renal disease and for microalbuminuria.<sup>13</sup> Factors influencing prognosis in hypertension are shown in Table 1.

## 3. Hypertension as a Cause/Consequence of Chronic Renal Failure

Essential hypertension complicated by malignant phase, and renal artery atheroma with renal ischaemia or cholesterol embolisation are important causes of ESRF. Accelerated hypertension is synonymous with malignant hypertension, i.e., severe hypertension with fundal striate haemorrhages and “soft” exudates with or without papilloedema. Development of accelerated phase, whatever the cause, may lead to rapidly progressive renal failure, but accelerated hypertension as a complication of essential hypertension is no longer common in developed countries. In an analysis of 83 patients with accelerated hypertension, we found an underlying cause (usually renal) for the hypertension in 80% of cases.<sup>14</sup>

The relationship of “benign” (a misnomer) essential hypertension to renal failure is less clear. Classically in essential hypertension, there is increase in afferent arteriolar resistance, with a lesser increase in efferent resistance, so renal blood flow (RBF) decreases, filtration fraction (FF) increases and glomerular filtration (GFR) tends to be preserved.<sup>15</sup> GFR falls with age in normal subjects and this fall may be exacerbated in hypertension. In a study of untreated patients with “benign” essential hypertension

[diastolic blood pressure (DBP) <120 mm Hg], Reubi<sup>16</sup> found only minor changes in renal haemodynamics, indistinguishable from ageing changes. Even with profound elevations of DBP (120 to 150 mm Hg), renal function deteriorated only minimally in the absence of grade III to IV retinopathy (accelerated hypertension).

In some 10,000 autopsies, Zollinger<sup>17</sup> attributed only 11 cases of renal shrinkage to benign arteriosclerosis, 7 of which had severe renal artery atheroma. Kincaid-Smith and Whitworth undertook 131 consecutive autopsies on patients with BP >180/110 mm Hg but no retinal haemorrhages or exudates, finding no reduction in renal size and hyalinised glomeruli only rarely.<sup>18</sup>

The major treatment trials in essential hypertension are all characterised by a paucity of renal failure endpoints. There is little or no evidence from large-scale randomised clinical trials of antihypertensive therapy in subjects without pre-existing renal disease that antihypertensive therapy modifies the very low risk of such patients developing renal failure. A link between “benign” hypertension and chronic renal failure (CRF) was not supported by a meta-analysis of prospective hypertension treatment trials reporting renal impairment as an outcome.<sup>19</sup>

Before “benign” hypertension can be considered as the cause of renal failure, there should be appropriate investigation with definition of macroscopic and microscopic renal and renovascular anatomy. Studies attributing renal impairment to essential hypertension often do not report urine microscopy findings, or use inappropriate criteria, raising the possibility that the “essential” hypertensives include patients with underlying renal parenchymal disease.<sup>20-22</sup> The use of normal serum creatinine concentration to exclude intrinsic renal disease may not detect decreases in GFR of less than 50%, and in any event hypertension as a consequence of renal disease does not necessitate impaired GFR – e.g., blood pressure (BP) falls with remission of nephrosis in minimal change disease.<sup>23</sup> A diagnosis of hypertensive nephrosclerosis is frequently made without biopsy, and without evidence that hypertension preceded the renal impairment. In a series of biopsied patients with “hypertensive nephrosclerosis”, blood pressure did not correlate with morphology, nor vascular sclerosis with glomerulosclerosis.<sup>24</sup>

Recently, Kincaid-Smith hypothesised that obesity and the insulin resistance syndrome play a major role in ESRF attributed to hypertension, and labelled hypertensive nephrosclerosis.<sup>25</sup> She pointed out that the pathology of the kidney in hypertension has changed – studies 50 years ago did not show segmental glomerulosclerosis, the key lesion in obesity, but it is now the key lesion in hypertensive nephrosclerosis. Other aetiological possibilities include lead and cocaine.<sup>19</sup>

Table 1. Factors Influencing Prognosis<sup>1</sup>

Risk factors for cardiovascular disease	Target-organ damage (TOD)	Associated clinical conditions (ACC)
Levels of systolic and diastolic blood pressure (grades 1-3)	Left ventricular hypertrophy (electrocardiogram or echocardiogram)	Diabetes
Males >55 years	Microalbuminuria (20 to 300 mg/day)	Cerebrovascular disease
Females >65 years	Radiological or ultrasound evidence of extensive atherosclerotic plaque (aorta, carotid, coronary, iliac and femoral arteries)	Ischaemic stroke
Smoking	Hypertensive retinopathy grade III or IV	Cerebral haemorrhage
Total cholesterol >6.1 mmol/L (240 mg/dL) or LDL-cholesterol >4.0 mmol/L (160 mg/dL)*		Transient ischaemic attack
HDL-cholesterol M <1.0, F <1.2 mmol/L (<40, <45 mg/dL)		Heart disease
History of cardiovascular disease in first-degree relatives before age 50		Myocardial infarction
Obesity, physical inactivity		Angina
		Coronary revascularisation
		Congestive heart failure
		Renal disease
		Plasma creatinine concentration:
		Females >1.4 mg/dL
		Males >1.5 mg/dL (120, 133 µmol/L)
		Albuminuria >300 mg/day
		Peripheral vascular disease

\* Lower levels of total and LDL-cholesterol are known to delineate increased risk but they were not used in the stratification table.

F: female; HDL: high-density lipoprotein; LDL: low-density lipoprotein; M: male

### *Hypertension Associated with Renal Failure — The Role of Early Life*

There is a significant body of evidence suggesting that early life influences, particularly intrauterine influences, can determine subsequent hypertension.<sup>26,27</sup> Brenner and Chertow<sup>28</sup> suggested that intrauterine growth retardation might be associated with impaired nephrogenesis, ultimately leading to hypertension and increased risk of cardiovascular and renal disease. There are also observational data in humans and experimental studies which support this view, although the importance of low birth weight per se is uncertain.<sup>29,30</sup>

### *Hypertension as a Consequence of Renal Abnormalities*

Detailed discussion of this topic is beyond the scope of this review. Possible mechanisms include activation of renal sympathetics, volume expansion, sodium retention, increased vasoconstriction through e.g., angiotensin, aldosterone, endothelin, vasopressin, or decreased vasodilation through e.g., nitric oxide, prostanoids. Various rare nephron segmental defects also cause hypertension e.g., Liddle's syndrome results from constitutive activation of distal tubular amiloride sensitive epithelial sodium channels and pseudohypoaldosteronism type 2 from mutations in the WNK family of serine-threonine kinases in the distal nephron.<sup>31</sup>

There is evidence both clinically and experimentally that "blood pressure goes with the kidney".<sup>32</sup> Normotensive recipients of kidneys from hypertensive donors become hypertensive and hypertensive recipients of normotensive kidneys may become normotensive. Family studies show higher blood pressures in first-degree relatives of patients

with primary glomerulonephritis or diabetic nephropathy. Thus, genetic predisposition to hypertension increases the risk of developing renal disease.<sup>32</sup>

### **4. Hypertension in the Progression of Experimental Renal Diseases**

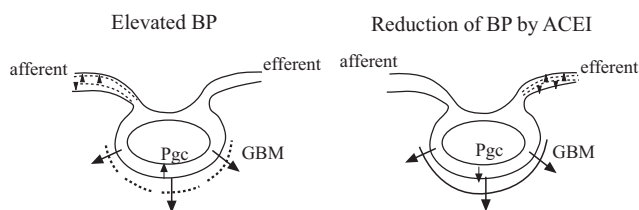
There is considerable species variation in the natural history of human and experimental (dog, rabbit, rat) renal disease.<sup>33</sup> There is much experimental evidence that hypertension promotes the progression of renal disease, including nephrotoxic nephritis in SHR, DOCA-salt on immune complex nephritis and Goldblatt hypertension on nephrotoxic nephritis.<sup>34-37</sup> It is likely that both systemic and intraglomerular hypertension are important.<sup>38</sup>

The rat partial renal ablation model is characterised by hypertension, proteinuria, and azotaemia, increased glomerular size, increased mesangial matrix and progressive glomerular hyalinisation and sclerosis.<sup>39</sup> Renal plasma flow is increased consequent to decreased afferent and efferent arteriolar resistances. Vasodilation of preglomerular capillaries allows systemic pressure to be transmitted to glomerular capillaries, producing glomerular hypertension. Single-nephron GFR is increased, due in the main to the increase in glomerular capillary pressure. Renal autoregulation is impaired, increasing vulnerability of the remnant kidney to elevated blood pressure. Renoprotection in this remnant kidney model correlates directly with continuous 24-hour systolic blood pressure.<sup>40</sup>

Brenner has hypothesised that decline in renal function relates to hyperfiltration in remnant nephrons.<sup>41,42</sup> Reduction of systemic blood pressure with drugs retards the rate of progression and structural changes in the remnant kidney.

Numerous studies have shown that functional and structural damage in the rat remnant kidney model of CRF is ameliorated by early treatment with angiotensin-converting enzyme inhibitors (ACEIs),<sup>42-44</sup> although this protection is not seen after proteinuria and glomerulosclerosis are established.<sup>43</sup> ACEIs not only lower systemic blood pressure, but in experimental animal models exert direct effects at the glomerular level by reducing capillary hypertension and glomerular hypertrophy, both of which may play a role in the genesis of glomerulosclerosis and CRF.<sup>42,44</sup> In addition to lowering systemic blood pressure, ACEIs prevent glomerular hypertension by reducing efferent arteriolar resistance (Fig. 1). Glomerular lesions were reduced in enalapril-treated rats compared with those receiving conventional treatment (with reserpine, hydralazine, and hydrochlorothiazide) despite equivalent control of systemic blood pressure. ACEIs improve size selectivity and hydraulic permeability of glomerular capillaries in the remnant kidney leading to reduction of proteinuria. However, in the study of Bidani et al,<sup>40</sup> the correlation of renoprotection with blood pressure was independent of RAS blockade, stressing the importance of systemic blood pressure. Studies of angiotensin II-induced renal injury<sup>45</sup> and 2 kidney 1 clip hypertension emphasise the importance of systemic blood pressure lowering in renal protection.<sup>46</sup> Similarly, L-NAME-induced exacerbation of hypertensive nephrosclerosis in SHR is reversed by ACEIs, angiotensin receptor blockers (ARBs) and calcium antagonists (but not diuretics).<sup>47</sup>

Dietary protein restriction limits the increase in glomerular capillary pressure by limiting the fall in preglomerular resistance.<sup>48</sup> These changes are associated with the reduction of morphological changes. Protein restriction and ACEIs



#### Elevated blood pressure (BP)

Afferent arteriolar dilation leads to increased renal plasma flow and transmission of systemic pressure to glomerular capillaries, causing glomerular hypertension. Increased glomerular capillary pressure (Pgc) causes hyperfiltration and glomerular basement membrane (GBM) permselectivity falls.

#### Reduction of BP by angiotensin-converting enzyme inhibitor (ACEI)

ACEIs lower systemic pressure and dilate the efferent arteriole, leading to reduction of glomerular pressure and reduction of glomerular hyperfiltration. Permselectivity increases and proteinuria falls.

Fig. 1. Adaptive changes in remnant nephrons after subtotal nephrectomy.

appear to preserve renal function by different mechanisms. We examined whether the effects of protein restriction and ACEIs on the progression of renal failure are common or additive. Protein restriction, enalapril or felodipine treatment all retarded progression of renal failure and development of glomerular lesions. Protein restriction and enalapril appeared to have additive effects in preventing glomerular sclerosis.<sup>49</sup>

ACEIs may also work through other mechanisms, in particular effects on tissue growth and fibrosis e.g., reducing expression of elevated cytokine and collagen mRNA and reducing interstitial infiltrates and collagen deposition. However these actions are likely to be less important than that of BP lowering.

As ACEIs and ARBs have different mechanisms of action, they might act synergistically. However, for equal blood pressure control, the combination does not appear to have advantages over either treatment alone in progression in the rat renal ablation model.<sup>50</sup>

## 5. Hypertension in the Progression of Renal Disease and Chronic Renal Failure

Hypertension has long been recognised as a poor prognostic feature in renal disease.<sup>51-54</sup> There is a very large body of evidence that not only accelerated hypertension but also benign hypertension accelerates the progression of renal disease.<sup>36,55</sup> Further, lowering blood pressure is known to slow the rate of deterioration of renal failure.<sup>56-58</sup> In accelerated hypertension, the renal survival of patients with underlying renal disease is worse than that of those with essential hypertension.<sup>14,56</sup>

In epidemiologic studies, levels of both systolic and diastolic hypertension relate to the deterioration of renal function, with systolic hypertension the more important.<sup>59</sup> In the Modification of Diet in Renal Disease (MDRD) Study, the prevalence of hypertension varied inversely with GFR.<sup>60</sup> The GISEN group found that in patients with progressive chronic nephropathies, systolic BP and pre-treatment morning BP measurements are the most reliable predictors of disease outcome.<sup>61</sup> The feasibility study for the MDRD found a correlation between the level of blood pressure and the progression of renal failure using isotopic measurement of GFR.<sup>62</sup> Similar findings were obtained using serum creatinine measurements.<sup>57</sup> In another study, lowering diastolic blood pressure to less than 90 mm Hg was associated with a slower rate of decline in GFR, as measured by the slope of reciprocal serum creatinine, in a large group of patients who ultimately progressed to ESRF.<sup>63</sup>

Some studies have not found a correlation between blood pressure and the progression of renal failure.<sup>64,65</sup> However, a single blood pressure reading may not be indicative of

24-h blood pressure load. Vetter and co-workers<sup>66</sup> reported that higher DBP did not correlate with progression. However, in this study, almost half the intermittently hypertensive subjects had significant renal function deterioration while they were hypertensive. In studies using ambulatory blood pressure monitoring, non-dippers (reduced nocturnal blood pressure fall) had accelerated progression compared with dippers.<sup>32</sup>

In the RENAAL study, baseline systolic blood pressure (SBP) of 140 to 159 mm Hg significantly increased risk for ESRD or death by 38% compared with those below 130 mm Hg.<sup>67</sup> In a multivariate model, every 10-mm Hg rise in baseline SBP significantly increased the risk for ESRF or death by 6.7%. Baseline SBP was a stronger predictor than DBP of renal outcomes in those with nephropathy due to type 2 diabetes. Those with the highest baseline pulse pressure had the highest risk for nephropathy progression but also the greatest risk reduction with SBP lowered to less than 140 mm Hg.<sup>67</sup>

There is strong evidence for an important role for hypertension in chronic kidney graft failure. Opelz and co-workers<sup>68</sup> studied the influence of blood pressure post-transplantation on long-term kidney graft outcome in nearly 30,000 patients. Increased levels of systolic and diastolic blood pressure post-transplantation were significantly associated with a graded increase of subsequent graft failure, and increased blood pressure was an independent risk factor for graft failure.<sup>68</sup>

Genetic predisposition may play a role. African-Americans have a higher incidence of CRF reportedly due to hypertension than Caucasians, although some of this might reflect investigation or presentation bias where the former are less likely to have underlying renal disease diagnosed. Various genetic polymorphisms have been reported to contribute to CRF, including some linked to hypertension and the renin-angiotensin system e.g., angiotensinogen M235T, ACE insertion/deletion (I/D). The A1166C polymorphism has been linked to susceptibility to faster progression of CRF, independent of relevant co-variables e.g., systolic blood pressure.<sup>69</sup> These relationships are controversial and require confirmation in large populations.

## 6. Treatment of Hypertension in Retarding Progression

It has long been known that aggressive blood pressure control can halt and even reverse renal impairment in patients with malignant hypertension, particularly in the absence of underlying intrinsic renal disease<sup>14</sup> and in scleroderma renal crisis, where ACEIs have revolutionised management.<sup>70</sup> Similarly, treatment of “benign” hypertension has been known for decades to slow progression in both diabetic<sup>58</sup> and non-diabetic nephropathy.<sup>36,56,57</sup>

Data from the MDRD Study suggest that aggressive blood pressure reductions should be sought in patients with chronic renal failure and proteinuria.<sup>71</sup> In that study, the beneficial effects of strict blood pressure control on slowing progression were confined to patients with significant proteinuria and benefits were greater at increasing levels of proteinuria.

We undertook the first double-blind, controlled, prospective, randomised trial of the effect of the ACEI enalapril compared with placebo on the progression of renal disease in non-diabetic patients with severe chronic renal impairment.<sup>72</sup> A mixed-effects linear model and intention to treat analysis, taking into account the number of observations per patient, indicated that enalapril significantly reduced the rate of deterioration of renal disease as measured by isotopic glomerular filtration rate, reciprocal of plasma creatinine, or creatinine clearance. The renal protective effects of enalapril were shown to be additive to its antihypertensive effect when blood pressure was held constant. Proteinuria was reduced by enalapril and was slightly increased in the placebo-treated patients, a highly significant difference.

Since this study appeared, a number of other similar placebo-controlled studies have been published, and these have been synthesised in a meta-analysis of 1860 patients by Jafar and colleagues.<sup>73</sup> This analysis confirmed the benefits of ACEIs in preventing progression in non-diabetic chronic renal disease (although it should be noted that the ACEI group had a greater decrease in blood pressure). Polycystic kidney disease may be an exception — van Dijk and colleagues<sup>74</sup> could not detect any difference between enalapril and atenolol in retarding progression or modifying microalbuminuria. Again, these studies add weight to the primacy of systolic blood pressure lowering over other mechanisms.

## Choice of Drugs in Renal Disease

When studies have shown a greater reduction in endpoints with one or other drug class, that class is considered to have a compelling indication (Table 2). Comparisons have been made between the ability of different classes of drugs to slow the progression of nephropathies. In comparative studies, a greater reduction in proteinuria was seen with initial therapy with ACEIs or ARBs than other classes, in particular calcium channel blockers (CCBs).<sup>75,76</sup> Placebo-controlled trials have shown significant reductions in proteinuria and the slowing of progression of renal failure in both non-diabetic and type 1 diabetic nephropathies with ACEIs<sup>73,77</sup> and in type 2 diabetic nephropathy with ARBs.<sup>75,78,79</sup> There is a strong association between acute increases in serum creatinine (of around 30%) after initiation of ACEIs with long-term preservation of renal function.<sup>80</sup> Interestingly, there are studies suggesting that further

Table 2. Compelling Indications, Contraindications and Cautions for Specific Antihypertensive Drugs<sup>1</sup>

Compelling indications	Preferred drug	Reference for evidence	Primary endpoint
Renal disease			
Diabetic nephropathy type 1	ACEI	77	Progression of renal failure
Diabetic nephropathy type 2	ARB	75, 78, 79	Progression of renal failure
Non-diabetic nephropathy	ACEI	73	Progression of renal failure
Drug			
Contraindications			
ACEIs, ARBs	Pregnancy		
	Bilateral renal artery stenosis		
	Hyperkalaemia		

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers

decreases in proteinuria may be obtained with ACEIs at doses greater than that required for maximal blood pressure lowering.<sup>81</sup> Whether ACEIs and ARBs are similar in their effects on progression of renal damage in type 1 and type 2 diabetic nephropathy is not known and whether they are superior to other drugs (except  $\beta$ -blockers) in preventing major CV events is not clear.<sup>82</sup> These studies have not been powered to detect reduction in heart attack and stroke but there is every reason to believe that here, as in all other circumstances examined, reduction in BP will reduce CVD risk.

Given the very significant costs of treating end-stage renal failure, aggressive blood pressure lowering in these patients is likely to be very cost-effective. While the trials did not identify the optimal blood pressure target for such patients, based on clinical trial evidence, and extrapolation from epidemiological studies, a target of <130/<80 mm Hg seems appropriate.

Data from the Hypertension Optimal Treatment (HOT) Study and the UK Prospective Diabetes Study have confirmed the safety of aggressive lowering of systolic blood pressure.<sup>1</sup> Unfortunately, some three-quarters of patients with hypertension do not achieve optimal blood pressure.<sup>83</sup> This may be due to failure to diagnose hypertension; failure of patients or doctors to start and/or continue treatment; poor adherence to treatment by patients and to guidelines by doctors; and lack of adequate therapy.<sup>84,85</sup> It is also the case for treatment of hypertension in chronic renal failure.<sup>86</sup>

The major cause of morbidity and mortality in chronic renal disease is cardiovascular, not renal, and, to date, trials showing advantages for ACEIs and ARBs in preventing progression have not shown advantages over other classes in preventing cardiovascular endpoints. The totality of clinical trial data, in particular the meta-analyses from the BP Lowering Treatment Trialists Collaboration, indicates that the key to reduction of CVD risk (prevention of heart attack and stroke) is the lowering of blood pressure, rather

than the specific effects of the different classes of antihypertensive drugs.<sup>1,87</sup> In most cases, multiple drugs will be needed to control blood pressure optimally, and it is thus appropriate to use the full range of available drug classes to achieve optimal pressure, providing an ACEI or ARB is appropriate as part of the regime.

In summary, hypertension is a critical factor both in the progression of renal disease and the associated CVD morbidity and mortality, and blood pressure lowering is very effective in preventing the progression of these conditions.

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