Best practice for hypertensive patients with kidney disease

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Many patients with non-diabetic and diabetic renal disease undergo chronic renal function loss leading to dialysis or renal transplantation. The US National Kidney Foundation guidelines recommend that angiotensin-converting enzyme inhibitors and angiotensin type receptor antagonists are first choice therapy for these patients.

The development of strategies to slow the progression of chronic renal disease (CRD) is now considered one of the most important challenges facing nephrologists. In an editorial, Hostetter (2001) reported that in 2000, end-stage renal disease (ESRD) developed in over 90 000 patients in the USA, a figure approximately twice that of 10 years ago. If the trends of the past two decades persist, he estimates that approximately 175 000 new cases of uraemia and ESRD will be diagnosed in 2010. Caring for patients with ESRD already consumes more than $18 billion per year in the USA, with 6% of the Medicare budget used for this service. The majority of the growing renal disease problem is a result of the increasing incidence of type 2 diabetes worldwide, with a large proportion of such patients (~30%) developing diabetic nephropathy.

Irrespective of the cause of renal disease (whether the result of immune damage, diabetes, glomerular disease or hypertension), the loss of nephrons results in a common pathway of progressive renal function loss. Two important factors appear to play a role: intraglomerular pressure rise and loss of protein in the urine. Increased intraglomerular pressure leads to an accelerated loss of functioning nephrons, while excess protein loss damages both the glomerulus and tubule through metabolic 'overwork'. Strategies to stop progression are directed at reducing intraglomerular pressure and proteinuria.

Just reducing systemic blood pressure helps, since it reduces 'preload' for the glomerulus, thus reducing intraglomerular pressure as well. This is particularly important for patients with diabetes, because the glomerulus in these patients is very sensitive to slight increases in systemic blood pressure (possibly as a result of inadequate pre-glomerular vessel function).

Evidence for the benefits of controlling hypertension in the progression of renal disease is well established. The US National Kidney Foundation suggest that the blood pressure goal in patients with renal insufficiency and/or diabetes should be 130/80 mmHg. Observations of marked reductions in decline of the glomerular filtration rate after initiation of antihypertensive therapy in patients with type 1 diabetes (insulin-dependent) diabetic nephropathy by Mogensen (1976) and Parving et al (1983) first implied that hypertension contributed to the progression of CRD.

Much emphasis is placed on the treatment of people with diabetes since these are a group of patients known to be especially prone to develop end-organ damage if they have high blood pressure. It is estimated that kidney damage develops in up to one third of patients with type 1 (insulin-dependent) diabetes and approximately 25% of patients with type 2 (non-insulin-dependent) diabetes. Type 2 diabetes is the most common problem with 90–95% of all diabetic patients having type 2 diabetes.

But which antihypertensive agents are most effective in these patients? This review sets out to consider the latest evidence that drugs which antagonize or inhibit the synthesis of angiotensin II bring additional kidney protection beyond blood pressure control.

EARLY STUDIES IN TYPE 1 DIABETES

The first trials concentrated on the relatively small number of patients with type 1 diabetes, since it was considered the most clear-cut form to study. Bjorck et al (1992) showed that when the effect of an angiotensin-converting enzyme (ACE) inhibitor is compared with a beta blocker,

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the former showed additional benefits in protecting the kidney (measured with soft end points like loss of glomerular filtration power), despite blood pressure being reduced to the same level in both groups.

Lewis et al (1993) performed the first large randomized placebo controlled trial with hard end points, comparing captopril (ACE inhibitor) with placebo in 409 patients with type 1 diabetes. They showed that ACE inhibitor therapy was associated with a 50% reduction in the risk of the combined end point of death, dialysis and transplantation and that the benefits were independent of the small disparity in blood pressure between the two groups. The authors concluded that their results suggest that an ACE inhibitor slows the progression of type 1 diabetic nephropathy by a mechanism independent of its antihypertensive properties.

STUDIES IN NON-DIABETIC CHRONIC RENAL DISEASE

Several studies then investigated the potential for ACE inhibitors to provide 'extra' renal protection in non-diabetic CRD. A meta-analysis of these trials was published by Jafar et al (2001) showing that ACE inhibitors do indeed provide additional protection.

The most recent of these studies is the African American Study of Kidney Disease and Hypertension (AASK) (Wright et al, 1996), designed to compare the effect of first-line treatment with amlodipine (calcium channel blocker, CCB), ramipril (ACE inhibitor) or metoprolol (a beta-blocker) on the progression of kidney disease in African Americans with mild to moderate renal insufficiency.

The study, which started in 1995 and concluded in September 2000, recruited 1094 African Americans aged 18–70 years with hypertension and mild to moderate renal insufficiency (defined as baseline glomerular filtration rate 20–65 ml/min/1.73 m^2). None of the subjects had diabetes.

AASK concentrated on African Americans since they have a higher prevalence of more severe hypertension, are more sensitive to renal function loss than the general population and have been characterized as being salt sensitive and responsive to diuretic therapy. They are an ethnic group in which ACE inhibitors were traditionally thought less effective than other classes of drugs.

CCB arm halts trials

The National Institute of Health called an early halt to the CCB (amlodipine) arm of the AASK trial after an interim analysis showed that the CCB arm had significantly more renal events that the ACE inhibitor arm in proteinuric patients, as reported by Agodoa et al (2001). Final results of this trial, announced at the American Heart Association Conference in 2001 (Wright et al, 2002), showed that risk reduction of ESRD for people taking ACE inhibitors *vs* beta blocker was 22%, and for people taking ACE inhibitors *vs* CCBs was 38%.

AASK was not the only trial to have a CCB arm halted early. A few years earlier, the Appropriate Blood Pressure Control in Diabetes trial by Estacio et al (1998) in hypertensive patients with type 2 diabetics was stopped early because there were excess myocardial infarctions in the CCB (nisoldipine) arm compared to the ACE inhibitor (enalapril) arm.

BEYOND BLOOD PRESSURE LOWERING

Animal studies by Anderson et al (1986) using renal ablation indicated that treatments to reduce systemic blood pressure failed to prevent progressive proteinuria and glomerular lesions. However, using micropuncture techniques, they found that 12 weeks treatment with an ACE inhibitor (enalapril) maintained the mean glomerular transcapillary pressure gradient at near normal levels and dramatically limited the development of proteinuria and glomerular lesions.

Such studies lead to the conclusion that blood pressure lowering is not sufficient for good results, but that drugs that reduce the formation or effect of angiotensin II also need to be used. In a review Wolf (1998) noted that in addition to its vasoconstrictor effects, angiotensin II has been shown to act as a profibrogenic cytokine, as a growth factor and to exhibit inflammatory properties. Angiotensin II stimulates fibronectin and collagen type I synthesis in cultured mesangial cells, partly through the synthesis and activation of transforming growth factor-β. It also stimulates transcription of collagen type IV in a proximal tubular cell line, and via modulation of the plasmin protease system angiotensin II may also accelerate renal fibrosis. Angiotensin II has the capacity to modify renal growth processes via the induction of a number of cytokines and growth factors in a variety of renal cells. Finally angiotensin II has been shown to impair tubular nitric oxide synthesis and to stimulate mesangial monocyte chemoattractant protein-1, thereby promoting renal monocyte/macrophage infiltration, a crucial factor in the progression of renal disease.

In addition to the AASK study a number of studies in patients with various underlying renal diseases have indicated that ACE inhibitors provide protection against the progression of renal insufficiency. In 1996 Maschio et al published findings of a 3-year trial (the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) Study) involving 583 patients with either glomerulopathies, interstitial nephritis, nephrosclerosis, polycystic kidney disease, diabetic nephropathy or unknown renal disorders. Patients (male and female between the ages of 18 and 70 years) were randomized to benazepril or placebo. Benazepril was not found to be effective in polycystic disease but in all other renal diseases it reduced the risk of reaching the study end point to 53%.

In the mid-1990s the group Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN) performed the Ramipril Efficacy In Nephropathy (REIN) trial (The GISEN Group, 1997) which targeted chronic non-diabetic nephropathies and addressed whether glomerular protein traffic influences renal disease progression. A total of 352 patients were classified according to their baseline proteinuria and were randomly assigned either ramipril or placebo plus conventional antihypertensive therapy to maintain diastolic blood pressure under 90 mmHg. They found that proteinuria was reduced and the decline in glomerular filtration rate per month was significantly lower in the ramipril group than in the placebo group, to an extent that seems to exceed the reduction expected for the degree of blood-pressure lowering.

STUDIES ON TYPE 2 DIABETICS

The Heart Outcomes Prevention Evaluation study investigators (2000) included 3577 patients with diabetes aged 55 years or older, who had a previous cardiovascular event or risk factor, were not taking ACE inhibitors and had no clinical proteinuria, heart failure or low ejection fraction. They were randomly assigned ramipril (10 mg/day) or placebo. The study was stopped 6 months early (after 4.5 years) because of a consistent benefit of ramipril compared with placebo. Ramipril lowered myocardial infarction by 22%, stroke by 33%, cardiovascular death by 37%, and overt nephropathy by 24% but had no long-term effect on glycaemic control. The authors concluded that ramipril reduced the risk of cardiovascular events to a greater extent than could be attributed to its effect on blood pressure. They also stated that the benefit was apparent irrespective of whether patients had a history of cardiovascular events, hypertension or microalbuminuria, or were taking antihyperglycaemic agents.

Most recently the focus of trials has shifted to the much larger group of hypertensive patients with type 2 diabetes. Unsurprisingly these studies are being conducted with angiotensin II (type 1) receptor antagonists (AIIAs), a newer class of drugs that specifically reduces the effect of angiotensin II by blocking the receptor. The advantage of this class over ACE inhibitors is that they appear to have less side effects and are likely to help patients stay on therapy longer.

Two separate outcomes studies published in the same issue of the *New England Journal of Medicine* in September 2001 demonstrated that two different AIIAs had a significant effect on delaying the progression of kidney disease among patients with type 2 diabetes.

In the first study, the Irbesartan Diabetic Nephropathy Trial, Lewis et al (2001) compared the effects of an AIIA (irbesartan), a CCB (amlodipine) and placebo, with all patients receiving other antihypertensive medications to control blood pressure (that excluded ACE inhibitors, AIIAs and CCBs) in a group of 1715 men and women in the late stages of diabetic kidney disease. Investigators found that irbesartan reduced the risk of progressing to transplantation or dialysis by 26% when compared to placebo, and by 34% compared to amlodipine. Throughout the study proteinuria was significantly reduced in the AIIA group, but not in the CCB or placebo groups.

In the second trial, the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, Brenner et al (2001) randomized 1513 patients with type 2 diabetes to receive either the AIIA losartan or placebo, both taken with additional conventional antihypertensive treatments and followed for an average of 3.4 years. The primary end point of the study was a composite measure consisting of time to the first occurrence of either doubling of serum creatinine (a marker indicating more than 50% loss of kidney function), ESRD or death.

Investigators found that patients taking losartan plus conventional blood pressure therapy had a significantly reduced risk of reaching the primary composite end point of renal protection (16%) and of developing ESRD (28%) compared to those taking placebo and conventional blood pressure therapy. In addition, losartan also provided a cardioprotective benefit in the study with a significant 32% risk reduction in hospitalization for heart failure.

The study showed that losartan prescribed in conjunction with conventional antihypertensive therapy significantly reduced proteinuria by 35% compared to the placebo plus conventional antihypertensive therapy. Since the achieved blood pressures in both groups were comparable it was concluded that the renal protective effects of losartan went beyond its ability to lower blood pressure.

CLEAR CUT RESULTS?

It should be noted that while most trials supported the renoprotective effect of ACE inhibitors, Tamimi and El Nahas (2000) have indicated that some of these conclusions were based on small study numbers or inadequate analyses. For instance in the study reported by Lewis et al (1993), based initially on 207 patients receiving captopril and 202 receiving placebo, after 4 years follow-up only 37 patients remained in the captopril group and 26 in the placebo. In the patients who had different outcomes comparisons were made between 8 and 17 patients at 3 years and 1 and 3 at 4 years. Such small numbers do not allow rigorous statistical analyses.

In the AIPRI study differences in the systolic blood pressure between patients on benazepril and placebo were not adjusted for in the final analysis of the data. Such differences are known to protect from hypertension-induced vascular events and it is therefore difficult to determine whether the improved outcome was the result of specific renal protective effects of ACE inhibition, or of the substantial reduction in blood pressure achieved by benazepril.

In the REIN study the antiproteinuric effect of ACE inhibitors was only seen at mean arterial pressures greater than 100 mmHg; below that there was no difference in proteinuria between ramipril- and placebo-treated patients. However, as Tamimi and El Nahas (2000) conclude, the renoprotective effects of ACE inhibitors may be the result of effective 24-hour blood pressure control, a factor not measured in these trials. Nevertheless the overall conclusion of such trials is that ACE inhibitors do have additional protective properties against the progression of glomerulosclerosis compared with other antihypertensive agents.

MECHANISM OF ACTION

Why do ACE inhibitors and AIIAs appear to show a renal protective effect going beyond blood pressure control when compared to other antihypertensive drugs, including CCBs? The reason, as noted above, may be that angiotensin II appears to be a crucial hormone in multiple actions that promote loss of renal function such as increasing the pressure in the glomerulus, increasing the proteinuria and promoting the growth of (kidney) tissue. By reducing the action of angiotensin II (either by reducing its formation or by blocking its receptor) these actions are minimized, preventing the eventual loss of nephrons.

ECONOMIC ARGUMENTS

According to data from RENAAL (Gerth et al, 2002) presented at last year's American Society of Nephrology/International Society of Nephrology World Congress of Nephrology using ACE inhibitors and AIIAs makes good economic sense.

Losartan reduced the estimated number of days the average patient spent with ESRD by 30%. After factoring in the cost of losartan, researchers found that this saved $3000 per patient over 3.5 years and $4800 over 4 years. Extrapolating the results of the RENAAL study to the estimated 595 000 type 2 diabetic patients with proteinuria in the USA, losartan treatment could result in a $4.3 billion reduction in the cost of ESRD and a $2.9 billion net saving over 4 years.

CONCLUSIONS

The available evidence shows that physicians should be treating patients with kidney disease more aggressively using agents that antagonize or inhibit the action of angiotensin II as drugs of first choice. If blood pressure and/or proteinuria are not well controlled, diuretics should be introduced as second-line therapy, followed by increasing the dose of the ACE inhibitor or AIIA. If blood pressure is still not well controlled either beta-blockers or CCBs should be considered depending on the co-morbid conditions. Recent guidelines from the American Diabetic Association (2002) and the US National Kidney Foundation (2002) suggest that the same holds for both diabetic and non-diabetic renal disease patients.

The UK National Institute for Clinical Excellence has also produced two clinical guidelines addressing the screening and management of retinopathy and the prevention of renal disease in type 2 diabetes (http://www.nice.org.uk/article.asp?a=28193). The guidelines advocate that type 2 diabetics at high risk of renal disease should be prescribed ACE inhibitors which will slow the progression of diabetic nephropathy by a mechanism independent of their antihypertensive properties. The guidelines also support the

message that if an ACE inhibitor is not fully effective, a combination of drugs should be used.

There is, however, concern that the message is not getting through to all clinicians. Kausz et al (2001) reviewed the charts of patients with kidney disease in five nephrology outpatient clinics from the Boston area and discovered that only 49% of these patients had been prescribed ACE inhibitors or AIIAs.

While current National Kidney Foundation guidelines recommend that CCBs are used no earlier than as third-line agents in hypertensive patients with kidney disease, since they demonstrate no additional renal protective effects, they are still widely prescribed as first-line therapy for hypertension in patients with renal disease

Although the studies show promise there is still a great deal to be done since patients develop ESRD despite treatment with three to four different antihypertensive drugs in combination with either an ACE inhibitor or AIIA treatment. The future challenge is to find better strategies to reduce blood pressure and/or the intraglomerular pressure and/or proteinuria more effectively. Combining ACE inhibition and AIIA may prove an interesting option since several studies, such as Russo et al (1999) and Mogensen et al (2000), have shown additive effects of such combinations on blood pressure and proteinuria.

With less than half of patients currently receiving optimum treatment it is clear that clinicians urgently need to be reviewing their practice according to the general and local guidelines. HM

Conflict of interest: Professor de Zeeuw is a RENAAL Steering Committee Member.

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KEY POINTS

- Pharmaceutical strategies to delay end-stage renal disease in patients with hypertension are considered an important challenge for nephrologists.
- Drugs that antagonize or inhibit the synthesis of angiotensin II bring additional kidney protection beyond blood pressure control.
- Kidney damage occurs in up to one third of patients with type 1 diabetes and approximately one quarter of patients with type 2 diabetes.
- Using angintensin-converting enzyme inhibitors and angiotensin II antagonists makes good economic sense in the long term.