Angiotensin Receptor Blockers and Type 2 Diabetic Nephropathy

a report by
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Diabetes poses a major public health problem, and its impact on resources will escalate in the next 25 years. By 2030, it is predicted that more than 350 million people worldwide will be suffering from diabetes (principally type 2 diabetes); this represents 4.4% of the world's population.[1] The emergence of this diabetes epidemic can be explained, in part, by an ageing population, a sedentary lifestyle and, particularly, by the incidence of obesity. Indeed, dramatic increases in obesity rates in children and adolescents mean that type 2 diabetes and its complications are no longer restricted to the middle-aged and elderly.

Long-term complications of diabetes include increased risk of cardiovascular disease and the development of small-vessel (microvascular) complications that can result in blindness from diabetic retinopathy and renal failure from diabetic nephropathy.

Natural History of Diabetic Nephropathy

Hypertension is a leading risk factor for chronic kidney disease (CKD). In people with diabetes, hypertension is highly prevalent, occurring twice as frequently as in those without diabetes. High blood pressure is also often present when diabetes is diagnosed and both conditions cause target organ damage, which includes the development of kidney disease in approximately one-third of patients. The first clinical evidence of renal damage is microalbuminuria (see *Table 1*), which not only carries a high risk of serious renal disease, but also is associated with significantly increased cardiovascular morbidity and mortality. Without adequate risk factor control at this early (incipient) stage (which must include the rigorous treatment of hypertension), urinary albumin excretion increases by approximately 10–20% each year.

Between 20% and 40% of type 2 diabetic patients with microalbuminuria will progress to overt nephropathy, with the macroalbuminuria contributing to further renal damage. At this stage, the extent of renal impairment is often evaluated in terms of the estimated glomerular filtration rate (GFR), based on serum creatinine concentrations. After 20 years of overt nephropathy, approximately 20% of patients will require a kidney transplant or dialysis because of end-stage renal disease indicated by a GFR of less than 15ml/min/1.73m^2.

Inevitably, the management of patients with end-stage renal disease places heavy demands on healthcare resources. Even more disconcerting is the fact that the majority of patients with diabetic nephropathy will have experienced a debilitating stroke, heart disease or peripheral artery disease, or will have died of cardiovascular disease, even before end-stage kidney disease develops.

The Relationship Between Systemic and Intraglomerular Blood Pressure

Evidence of renal damage is often found when diabetes is diagnosed, especially if the patient also has high blood pressure. In others, it is detected very soon afterwards. It is postulated that it is not the systemic blood pressure that determines the extent of the renal damage, but the pressure within the glomerular capillaries. A high systemic blood pressure can be associated with increased intraglomerular pressure, but glomerular hypertension can exist even in the presence of seemingly well-controlled hypertension. Elevated intraglomerular pressure leads to structural changes in the glomerulus, at least in part, as a result of oxidative stress and endothelial dysfunction. As the damage progresses, protein leakage increases until microalbuminuria becomes apparent. A vicious cycle ensues.

The advancing loss of glomeruli causes an adaptive elevation of glomerular pressure in an attempt to maintain the GFR. The kidney damage resulting from increased glomerular capillary pressure worsens systemic hypertension, resulting in further glomerular hypertension (see *Figure 1*).[2]

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1. *Wild S, Roglic G, Green A et al., "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030",* Diabetes Care *(2004);27: pp. 1,047–1,053.*

Table 1: Definitions of Urinary Protein Abnormalities

Definition	Spot Collections		Timed Collection	24-hour Collection
	Creatinine	Creatinine	Albumin	Albumin
Normoalbuminuria	<3.4mg/mmol	<30μg/mg	<20μg/min	<30mg/24h
Microalbuminuria (incipient nephropathy)	3.4–34mg/mmol	30–299μg/mg	20–199μg/min	30–299mg/24h
Macroalbuminuria (overt nephropathy)	≥34mg/mmol	≥300μg/mg	≥200μg/min	≥300mg/24h

The Importance of Systemic Blood Pressure Control

Meta-analysis of clinical trials in diabetic and non-diabetic renal disease has established a direct and continuous relationship between the achieved blood pressure and the decline in GFR with advancing renal impairment.[3] In patients with urinary albumin concentrations higher than 1g/24h and a GFR in the range of 13–55ml/min/1.73m^2, the optimal blood pressure is <125/75 millimetres of mercury (mmHg).[4]

Targeting the Renin–Angiotensin–Aldosterone System

Activation of the renin–angiotensin–aldosterone system (RAAS), which results in increased angiotensin II production, raises systemic blood pressure, a major contributor to renal disease initiation and progression. Angiotensin II also plays a central role in mediating pathophysiological changes in the kidney, such as interstitial fibrosis and glomerulosclerosis.

As renal disease progresses, there is further activation of the RAAS and circulating levels of angiotensin II are elevated in patients with diabetes and renal disease. For this reason, agents such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) that target the RAAS should logically be the antihypertensive agents of choice in patients with diabetic nephropathy. This is supported by a whole range of studies in both patients with type 1 and type 2 diabetes showing evidence for renal protection at various stages of the nephropathic process.[5]

Choosing Between an ACE Inhibitor and an ARB

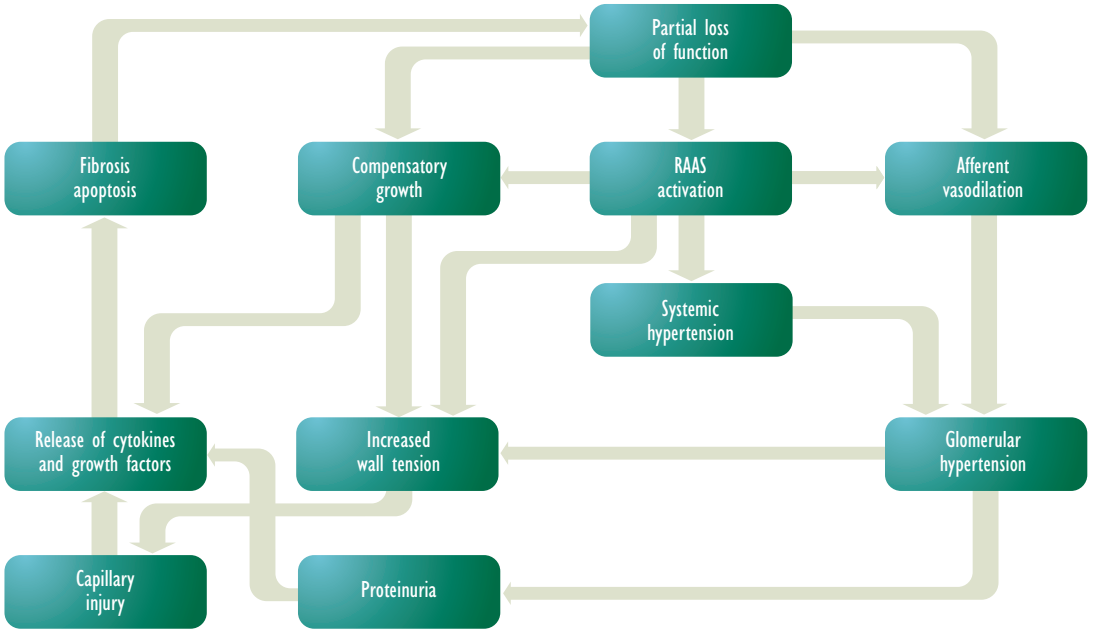
ACE inhibitors and ARBs act on the RAAS in different ways. ACE inhibitors prevent the conversion of angiotensin I to angiotensin II and block the breakdown of bradykinin and other vasoactive peptides. When used over prolonged periods, ACE inhibitors can be susceptible to 'ACE escape', in which there is a gradual return of angiotensin II to baseline levels.[6] In addition, angiotensin I can be converted to angiotensin II via non-ACE pathways. This is particularly true for the local kidney RAAS, by which up to 40% of angiotensin II formation is generated by non-ACE mechanisms. This may explain why ACE inhibitors do not reduce levels of angiotensin II in the renal interstitial fluid.

ARBs specifically block the angiotensin type 1 (AT_1) receptor, irrespective of how the angiotensin II is generated. This is in contrast to ACE inhibitors, which reduce the amount of angiotensin II available to activate both the AT_1 and AT_2 receptors. Activation of AT_2 receptors has antiproliferative effects and is thought to counteract the detrimental cell growth and vasopressor activity induced by AT_1 activation.[7]

There is potential for differences in the efficacy of ARBs and ACE inhibitors. It is also feasible that dual blockade of the RAAS may confer additional renoprotective benefits to monotherapy.

2. *Dworkin L D, Shemin D G, "The role of hypertension in progression of chronic renal disease", in: Schrier R W (ed),* Atlas of Diseases of the Kidney, *Blackwell Scientific, Malden (1999): pp. 6.1–6.18.*
3. *Bakris G L, Williams M, Dworkin L D et al., "Preserving renal function in adults with hypertension and diabetes: a consensus approach",* Am. J. Kidney Dis. *(2000);36: pp. 646–661.*
4. *Lazarus J M, Bourgoignie J J, Buckalew V M et al., "Achievement and safety of a low blood pressure goal in chronic renal disease",* Hypertension *(1997);29: pp. 641–650.*
5. *National Kidney Foundation, "K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease",* Am. J. Kidney Dis. *(2004);43: pp. S1–S290.*
6. *Sica D A, "Combination angiotensin-converting enzyme inhibitor and angiotensin receptor blocker therapy: its role in clinical practice",* J. Clin. Hypertens. *(2003);5: pp. 414–420.*
7. *Ruiz-Ortega M, Ruperez M, Esteban V et al., "Molecular mechanisms of angiotensin II-induced vascular injury",* Curr. Hypertens. Rep. *(2003);5: pp. 73–79.*

Figure 1: The Central Role of Systemic Hypertension in Renal Disease[2]



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Treatment Guidelines

The 2004 guidelines of the US National Kidney Foundation (NKF) recommend ARBs or ACE inhibitors to be used in all patients with diabetic nephropathy, regardless of their blood pressure – provided that neither ARBs nor ACE inhibitors are contraindicated – as part of a multi-intervention strategy.[5] This reflects the importance of blocking the RAAS and controlling systemic and intraglomerular blood pressure.

Despite the fact that the NKF recommendations do not distinguish between ACE inhibitors and ARBs, the large number of clinical trials conducted in diabetic (and, indeed, non-diabetic) renal disease have identified differences between the two classes of drugs in type 1 and type 2 diabetes.[5] The NKF guidelines conclude that both ACE inhibitors and ARBs are effective at slowing progression of microalbuminuria due to type 1 or 2 diabetes.

Although there is strong evidence that ACE inhibitors are more effective than other antihypertensive classes in slowing progression of macroalbuminuria in type 1 diabetes, there is only weak support for their superiority in overt type 2 diabetic nephropathy.[5]

In contrast, there is strong evidence that ARBs are more effective than other antihypertensives in slowing progression of overt type 2 diabetic nephropathy.

Clinical Evidence of ARB Efficacy

Support for the renoprotective efficacy of ARBs in type 2 diabetes is provided by data for losartan, irbesartan, valsartan and telmisartan. The efficacy of ARBs has been demonstrated both in patients with incipient nephropathy and with overt disease.

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA 2)[8] and the Microalbuminuria Reduction with Valsartan (MARVAL)[9] studies showed that ARB treatment for two years and 24 weeks, respectively, brought about reduction and, commonly, regression of microalbuminuria.

In the Diabetics Exposed to Telmisartan and Enalapril (DETAIL) study, lasting five years, patients with type 2 diabetes and early nephropathy (predominantly microalbuminuria) were evaluated.[10] Telmisartan provided comparable renoprotection with enalapril. The initial steep decline in the directly determined GFR was stabilised by both telmisartan and enalapril to

8. *Parving H H, Lehnert H, Brochner-Mortensen J et al., "The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes",* N. Engl. J. Med. *(2001);345: pp. 870–878.*
9. *Viberti G, Wheeldon N M, "Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect",* Circulation *(2002);106: pp. 672–678.*
10. *Barnett A H, Bain S C, Bouter P et al., "Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy",* N. Engl. J. Med. *(2004);351: pp. 1,952–1,961.*

approximately 2ml/min/1.73m^2/year after the third year of the trial.

The DETAIL study also demonstrated a much lower incidence of cardiovascular morbidity and mortality than predicted by epidemiological data in patients who were at very high cardiovascular risk; indeed, approximately half of the patients already had evidence of cardiovascular disease at trial entry. These benefits are postulated to be due, at least in part, to blockade of the RAAS by these agents.

In patients with urinary albumin excretion of more than 500mg/day, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study revealed that losartan, compared with placebo, brought about a 16% reduction in the risk of a doubling of serum creatinine, end-stage renal disease or death.[11]

Patients in the Irbesartan Diabetic Nephropathy Trial (IDNT) had somewhat higher levels of urinary albumin excretion (>900mg/day).[12] Irbesartan reduced the risk of the doubling of serum creatinine, end-stage renal disease or death by 20% compared with placebo, and by 23% compared with the calcium channel blocker amlodipine.

On-going Studies

In the Renin Angiotensin System Study of Diabetic Nephropathy (RASS), the effect of losartan with or without enalapril is being evaluated to determine whether dual blockade of the RAAS using an ARB and an ACE inhibitor confers additional renoprotection.[13]

The Randomised Olmesartan And Diabetes Microalbuminuria Prevention (ROADMAP) study is assessing the effect of the ARB on onset of microalbuminuria in patients with type 2 diabetes.[14]

The renoprotective efficacy of telmisartan is being extensively studied within the Programme of Research to show Telmisartan End-organ Protection (PROTECTION).[15] One study is comparing the effect of telmisartan with that of the ACE inhibitor ramipril on one of the earliest markers of damage to the renal vasculature – endothelial dysfunction – in patients with type 2 diabetes with normo- or microalbuminuria. Two studies are comparing the renoprotective efficacy of long-acting telmisartan with that of either losartan or valsartan in overt type 2 diabetic nephropathy. A fourth study is assessing the effect of different doses of telmisartan on incipient type 2 diabetic nephropathy.

Despite the fact that the NKF recommendations do not distinguish between ACE inhibitors and ARBs, ... clinical trials have identified differences between the two classes of drugs in type 1 and type 2 diabetes.

Conclusions

Existing evidence strongly supports the use of ARBs for the prevention of type 2 diabetic nephropathy progression. There is currently little direct comparison of the efficacy of ARBs with varying pharmacological features in the management of diabetic nephropathy. This is being addressed in on-going studies. ■

11. *Brenner B M, Cooper M E, de Zeeuw D et al., "Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy",* N. Engl. J. Med. *(2001);345: pp. 861–869.*
12. *Lewis E J, Hunsicker L G, Clarke W R et al., "Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes",* N. Engl. J. Med. *(2001);345: pp. 851–860.*
13. *Mauer M, Zinman B, Gardiner R et al., "ACE-Is and ARBs in early diabetic nephropathy"* J. Renin Angiotensin Aldosterone Syst. *(2002);3: pp. 262–269.*
14. *Halimi S, "Primary cardiorenal prevention in patients with type-2 diabetes. The Roadmap study",* Presse Med. *(2005);34: pp. 1,300–1,302.*
15. *Weber M, "The telmisartan Programme of Research tO show Telmisartan End-organ proteCTION (PROTECTION) programme",* J. Hypertens. *(2003);21(suppl. 6): pp. S37–S46.*