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Inhibition of the renin-angiotensin system in diabetic patients – beyond HOPE

ANTHONY H BARNETT

Abstract

Treatment to reduce blood pressure is effective in preventing and slowing the progression of the vascular complications of diabetes. Recent studies have suggested that use of antihypertensives that inhibit the renin-angiotensin system may have particular benefit in patients with type 2 diabetes in terms of cardiovascular and renal protection. Present practice is to use angiotensin-converting enzyme (ACE) inhibitors as first-line agents, with angiotensin II receptor antagonists (AIIAs) as back-up drugs in the event of side effects or intolerance. The findings of recent trials with AIIAs, however, suggest that they are an equivalent class of drugs to the ACE inhibitors from the point of view of renal profile and that their better side-effect profile could also make them suitable first-line drugs for patients with microalbuminuria and overt nephropathy.

Key words: renin-angiotensin system, hypertension, diabetes, angiotensin II receptor antagonist, microalbuminuria, nephropathy.

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Anthony H Barnett

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Introduction

Cardiovascular disease kills more than three-quarters of patients with type 2 diabetes, many prematurely. If we are to make an impact on type 2 diabetes this is where we need to focus. Risk factors include diabetes *per se*, dyslipidaemia, cigarette smoking and hypertension. Hypertension, in particular, is much more common in the diabetic compared with the general population. Indeed, more than 70% of patients with type 2 diabetes are hypertensive and this accelerates development of both macrovascular (myocardial infarction [MI], stroke) and microvascular (neuropathy, retinopathy and nephropathy) complications of diabetes.[1] In these patients, treatment to reduce blood pressure (BP) has been shown to be effective in prevention and slowing of progression of vascular complications.[1] More recently, a number of studies have suggested particular benefit from the point of view of cardiovascular and renal protection by approaches which include use of agents that inhibit the renin-angiotensin system (RAS).

Undergraduate Centre, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS.
Anthony H Barnett, Professor of Medicine and Consultant Physician
Correspondence to: Professor AH Barnett
(email: anthony.barnett@heartsol.wmids.nhs.uk)

What did HOPE tell us?

The Heart Outcomes Prevention Evaluation (HOPE) study produced the most impressive data for the benefit of angiotensin-converting enzyme (ACE) inhibition on cardiovascular outcomes in diabetic patients.[2] More than 9,000 patients aged over 55 years with definite evidence of ischaemic heart disease, or diabetic patients with a previous cardiovascular event or at least one other cardiovascular risk factor, were randomly assigned ramipril 10 mg o.d. or placebo. The subjects could have any other medication, including antihypertensives, except for inhibitors of the RAS.

Ramipril was associated with reduced risk of cardiovascular death, MI, and total mortality in patients at risk for cardiovascular events but without heart failure. In the group of 3,500 people with diabetes, ACE inhibition was associated with risk reduction for cardiovascular deaths (37%), MI (22%), stroke (33%) and total mortality (24%) compared with placebo. This was achieved despite only small differences in BP between active and control groups. These results suggest that inhibition of the RAS is associated with cardiovascular protection in higher risk groups, an effect which is, at least in part, independent of BP lowering. This study also indicated that more work needs to be done to define the range of benefits available from modifying the RAS.

Other studies have demonstrated evidence for renal protection in both type 1 and type 2 diabetic patients by aggressive BP lowering and with particular benefit from ACE inhibitors, as well as supporting HOPE in suggesting cardiovascular benefit.[3] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS), for example, examined the effect of using the ACE inhibitor perindopril to lower BP in more than 6,000 patients with a history of cerebral haemorrhage, stroke, or transient ischaemic attack. The study found that perindopril in combination with indapamide reduced the risk of stroke by a highly significant 28%, even in patients without hypertension.[4]

More recently, it has been suggested that since ACE inhibition may not provide complete blockade of the RAS, an alternative approach might be to use a combination of ACE inhibitor and angiotensin II receptor antagonist (AIIA). The Candesartan and Lisinopril Microalbuminuria (CALM) study, for example, found that co-prescribing an ACE inhibitor with an AIIA provided both improved BP response and greater reduction in microalbuminuria.[5] Microalbuminuria defines an albumin excretion rate above the normal range but below the level of dipstick detection. It is itself a predictor of later development of overt diabetic nephropathy and is associated with a greatly increased cardiovascular risk for patients with type 2 diabetes.[1]

Angiotensin II antagonists (AIIAs)

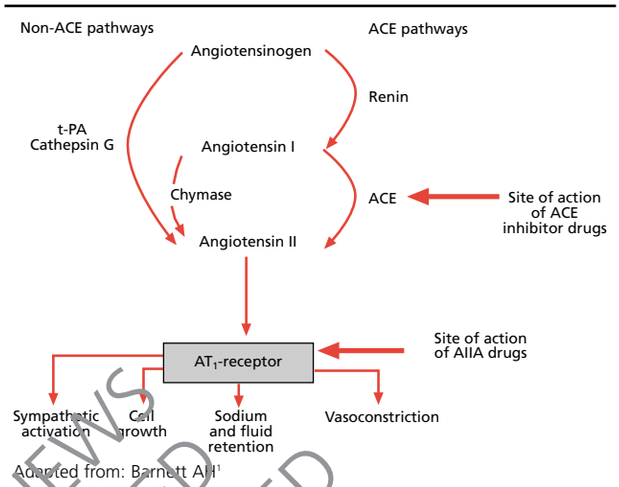
Despite the benefits of ACE inhibitors shown with HOPE and other studies, patients who could benefit might be denied these drugs because of side effects, such as cough and angio-oedema. A newer class of antihypertensives, the AIIAs, have similar efficacy to ACE inhibitors in terms of BP reduction but are generally better tolerated, with a side effect profile comparable to placebo.[6] These agents might have similar or even better long-term efficacy to ACE inhibitors since they block the RAS more completely. They act by specifically blocking the effects of angiotensin II at the type 1 receptor site (figure 1). Their mode of action also means they are much less likely to cause cough or angio-oedema than ACE inhibitors, with improved compliance.[7]

Similar long-term benefits of AIIAs to those shown with ACE inhibitors are yet to be proven but a number of trials are ongoing to determine the efficacy of AIIAs in preventing cardiovascular morbidity and mortality as well as studies more specifically on diabetic nephropathy. Table 1 summarises the AIIA studies in diabetic patients.

Improvements in cardiovascular and renal morbidity and mortality in diabetic patients – beyond HOPE?

Last year, the US Food and Drug Administration's Cardiovascular and Renal Drugs Advisory Committee recommended approval of the AIIA losartan for the treatment of nephropathy in type 2 diabetes on the basis of the Reduction of End points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study. This trial compared losartan 50–100 mg versus placebo in hypertensive type 2 diabetic patients.[8] There was a significant (16%, p=0.024) reduction in the risk of renal disease progression with losartan as measured by the primary composite end point – time to a doubling of the baseline creatinine level, end-stage renal disease and death.

Figure 1. The renin-angiotensin system and the site of action of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (AIIAs)



Adapted from: Barnett AH[1]

Two other trials, which involved the AIIA irbesartan, studied type 2 diabetic patients with overt diabetic nephropathy, the Irbesartan Diabetic Nephropathy Trial (IDNT) and those with incipient nephropathy – IRbesartan MicroAlbuminuria Type 2 Diabetes Mellitus in hypertensive patients trial (IRMA). Again, irbesartan showed evidence of renal protection from the point of view of slowing/prevention of progression from incipient to overt nephropathy (IRMA2) and also showed similar results to RENAAL in those with more advanced nephropathy. These trials have led to an extension of the licence for irbesartan as a treatment for renal disease in patients with diabetes and hypertension in Europe.

The three-year IDNT was a double-blind, randomised, multicentre trial comparing irbesartan versus the calcium channel blocker amlodipine versus placebo.[9] Irbesartan was demonstrated to have two key nephroprotective effects. First, it reduced the risk of renal function decreasing by 50% compared with placebo; progression to dialysis or transplantation was reduced by 26% versus placebo. For the primary composite end point – time to a doubling of the baseline creatinine level, end-stage renal disease and death – the irbesartan group had a relative risk reduction of 20% compared with placebo (p=0.02) and 23% compared with amlodipine (p=0.006).

The IRMA II trial looked at the effect of irbesartan (300 mg and 150 mg) versus placebo on microalbuminuria in a different group of hypertensive type 2 diabetic patients, those with microalbuminuria but with normal creatinine, to see if this AIIA could slow progression of renal disease.[10] Irbesartan 300 mg showed a significant risk reduction of 65% (p<0.001) for the time to onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens. In all three IRMA II study groups BP was controlled to almost the same extent, suggest-

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Table 1. Trials testing angiotensin II receptor antagonists (AIIAs) in diabetic patients

Trial	Name	AIIA involved	Study population	Results
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan	Losartan (Cozaar®)	1,513 hypertensive type 2 diabetic patients with proteinuria above 500 mg/day and elevated serum creatinine	Reported 2001
IDNT	Irbesartan Diabetic Nephropathy Trial	Irbesartan (Aprovel®)	1,715 hypertensive type 2 diabetic patients (BP > 135/85 mmHg) with normal or raised creatinine and proteinuria above 900 mg/24 hour	Reported 2001
IRMA II	IRbesartan MicroAlbuminuria type 2 diabetes mellitus in hypertensive patients	Irbesartan (Aprovel®)	590 patients with type 2 diabetes, hypertension (BP > 135/85 mmHg) and microalbuminuria (albumin excretion rate 20–200 µg/min) and normal renal function	Reported 2001
MARVAL	Microalbuminuria Reduction with Valsartan	Valsartan (Diovan®)	332 patients with type 2 diabetes and microalbuminuria with or without hypertension	Reported 2002
NIDDM ABCD-2V	Appropriate Blood Pressure Control in Diabetes – with Valsartan	Valsartan (Diovan®)	Approximately 800 normotensive and hypertensive patients with type 2 diabetes	Results expected 2004
DETAIL	Diabetics Exposed to Telmisartan And enalaprIL	Telmisartan (Micardis®)	252 patients with type 2 diabetes and mild-to-moderate hypertension with proteinuria ranging from 10–1,000 µg/min	Results expected 2004
ONTARGET	ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial	Telmisartan (Micardis®)	23,400 patients with established coronary artery disease, stroke, peripheral vascular disease, or diabetes with end-organ damage	Results expected 2006/ 2007

ing that benefits observed were independent of BP reduction.

The MicroAlbuminuria Reduction with VALsartan (MARVAL) study, which reported in August 2002, was designed to evaluate the BP-independent effect of the AIIA valsartan versus the calcium blocker amlodipine on urinary albumin excretion (UAER) in type 2 diabetic patients with microalbuminuria, with or without hypertension.[11] The change in UAER at 24 weeks demonstrated a 44% reduction compared with baseline with valsartan and only 8% of baseline with amlodipine ($p<0.001$). Valsartan lowered microalbuminuria in patients with hypertension and in those who were normotensive. These effects were partly related directly to BP control but are also (in part) independent of its antihypertensive properties.

These four trials confirm that AIIAs can be considered as first-line treatment in any diabetic patient with microalbuminuria, as they are clearly renal protective across a wide continuum of renal dysfunction. As yet, there is no evidence that they are superior to ACE inhibitors in these patients.

A number of trials are expected to provide new insights into the optimal treatment of diabetic patients with hypertension. Two trials which included the AIIA telmisartan are particularly interesting as they are the only ones to include an ACE inhibitor comparator.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is a large (28,400 patients, 793 centres, 40 countries) long-term (5.5 years) study.[12] It will compare the benefits of the ACE inhibitor ramipril, the AIIA telmisartan, and treatment with ramipril and telmisartan together, in a study population with established coronary artery disease, stroke, peripheral vascular disease, or diabetes with end-organ damage. Patients with congestive heart failure will be excluded. The primary end point for the trial is a composite of cardiovascular death, MI, stroke, and hospitalisation for heart failure. Secondary end points will investigate reductions in the development of diabetes mellitus, nephropathy, dementia, and atrial fibrillation.

The Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) trial, which is expected to report this year, compares the AIIA

Key messages

- Treating diabetic hypertension is effective in preventing and slowing progression of vascular complications
- HOPE suggested that RAS inhibition is associated with cardiovascular protection in diabetic patients
- AIIAs block the RAS more completely than ACE inhibitors, offering similar efficacy but with a better side-effect profile
- Trials with AIIAs confirm they are renal protective across a wide continuum of renal dysfunction
- Two trials are comparing the effect of the AIIA telmisartan with the ACE inhibitors ramipril and enalapril, in diabetic patients with hypertension; in the meantime AIIAs can be considered to be equivalent to ACE inhibitors, albeit with better tolerability
- AIIAs are suitable first-line drugs for patients with both microalbuminuria and overt nephropathy

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telmisartan with the ACE inhibitor enalapril over five years in patients with type 2 diabetes and mild-to-moderate hypertension.[13] The primary end point is a change in glomerular filtration rate (GFR) at five years, while secondary end points include annual change in GFR, cardiovascular events and mortality. Study recruitment is taking place in 10 countries and will close this year.

Application of trial findings to systems of care

Trials with AIIAs in diabetic patients demonstrate slowing of progression of renal disease, which make them suitable first-line drugs for patients with both microalbuminuria and overt nephropathy. In microalbuminuric patients they reduce proteinuria similarly to ACE inhibitors. To date, no direct trials comparing ACE inhibitors and AIIAs have been reported; meta-analysis suggests that there is no significant improvement using AIIAs compared with ACE inhibitors for the relevant renal end points. Nevertheless, AIIAs can be considered to be an equivalent class of drug, albeit with a better side effect profile. For those type 2 diabetic patients with incipient or overt nephropathy, AIIAs have now become an evidence-based alternative to ACE inhibitors as first-line antihypertensive treatment. Further studies will more clearly define their potential roles in cardiovascular protection and in combination with ACE inhibitors.

Conflict of interest

Professor Barnett has been involved as a paid member of advisory boards, and has received payments for lectures from the following companies: BMS/Sanofi, Boehringer Ingelheim, Servier Laboratories Ltd, Aventis and Novartis.

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