Optimising management of patients with hypertension and diabetes

The importance of achieving optimal management of hypertension in patients with diabetes has moved up the healthcare agenda during the last few years. General practitioner George Kassianos reviews recent clinical studies and guidelines.

Abstract

Optimal management of hypertension and diabetes is essential if the cardiovascular and renal mortality and morbidity associated with this condition is to be reduced.

Recent guidelines from the National Service Framework for Diabetes and the Scottish Intercollegiate Guidelines Network are discussed. Recent studies (UKPDS, RENAAL and PRIME) looking at the contribution tight blood pressure control and angiotensin II receptor antagonists can make to the management of this hypertension in diabetics are also covered.

Finally, the author advises how primary care can implement guidelines in practice to give the best possible care to patients with diabetes.

Key words: diabetes, hypertension, blood pressure, guidelines, renal failure, angiotensin II receptor antagonists.

Results from several landmark trials, including the United Kingdom Prospective Diabetes Study (UKPDS),[1] demonstrate the major improvements that achieving optimal management of hypertension in patients with diabetes can achieve in mortality and morbidity. The first part of the National Service Framework (NSF) for Diabetes,[2] published in late December 2001, has now set targets for aggressive management of hypertension in patients with diabetes, in a similar way to the earlier Scottish Intercollegiate Guidelines Network (SIGN) clinical guideline[3] on the management of diabetes.

'Diabetes is the biggest single cause of kidney failure in the Western world'

George Kassianos

Assessing the risk

Hypertension is very common among patients with type 2 diabetes, with a prevalence of 40–60% over the age range of 45–75 years.[1] Hypertension not only increases the already high risk of cardiovascular disease (CVD) associated with type 2 diabetes, but it is also associated with deterioration in renal function. Diabetic nephropathy is a major and rising cause of renal failure accounting for 16% of those starting dialysis in the UK.[4] Once a patient is on dialysis, five-year survival rates vary between 6–27%.[5] About 40% of diabetics develop diabetic nephropathy making renal disease an important cause of morbidity and mortality among patients with diabetes. Diabetes is the biggest single cause of kidney failure in the Western world, accounting for more than 25% of all cases.[6]

Improving management

Lowering blood pressure (BP) has been shown conclusively to reduce stroke and coronary heart disease in the general population.[7] The UKPDS revealed that tight control of BP (average BP < 144/82 mmHg) was associated with a dramatic 44% reduction in stroke and a 37% reduction in microvascular end points compared with less tight BP control (< 154/87 mmHg).[1] This evidence, together with that from other studies, led the British Hypertension Society to set an optimal target BP for patients with diabetes of less than 140/80 mmHg.[8]

The NSF suggests a blood pressure target of 140/85 mmHg for high-risk patients, including those with diabetes. It warns: "In practice, it will not be possible to achieve this for every patient. However, practitioners should not be satisfied with pressures greater than 150 mmHg or 90 mg diastolic in these high risk groups." The British Hypertension Society recommends a target systolic of 140 mmHg in diabetic patients, similar to non-diabetics. Although difficult to achieve, we should make efforts to achieve these targets in view of the major benefits they offer to patients.

The NSF sets out standards relevant to the management of hypertension in patients with diabetes:

- Standard 4 of the NSF (Clinical care of adults with diabetes) stipulates that all adults with diabetes receive high-quality care throughout their lifetime,

including support to optimise the control of their blood glucose, blood pressure and other risk factors for developing the complications of diabetes. It points out that controlling raised blood pressure in diabetic hypertensives reduces their risk of developing both microvascular complications and cardiovascular disease.

- Standards 10 to 12 of the NSF call for the detection and management of long-term complications. Standard 11 says: "The NHS will develop, implement and monitor agreed protocols and systems of care to ensure that all people who develop long-term complications of diabetes receive timely, appropriate and effective investigation and treatment to reduce their risk of disability and premature death." One of the key recommendations is that tight blood pressure and blood glucose control in people with diabetic nephropathy can reduce the deterioration in renal function, in addition to the risk of cardiovascular disease.

These recommendations are similar to those published previously in the SIGN guidelines, which advise that hypertension in diabetics should be treated aggressively with lifestyle modifications and drug therapy to achieve a systolic blood pressure of less than 140 mmHg and a diastolic pressure of 80 mmHg or lower.

AIIRAs: optimising renal function while lowering blood pressure

The optimal strategy is to minimise deterioration in renal function at the same time as lowering blood pressure – this is the best way we can help our patients to achieve healthier lives. There is recent evidence that angiotensin II receptor antagonists (AIIRAs) protect renal function in patients with type 2 diabetes, with three major trials published in *The New England Journal of Medicine* in September 2001 showing for the first time that antihypertensive therapy with the AIIRAs, losartan and irbesartan, protected the kidney by significantly delaying the progression of kidney disease.

The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial showed that losartan reduced the risk of progression to end-stage renal disease (ESRD) or death by 20% (p=0.01). PRIME (PRogram for Irbesartan Mortality and morbidity Evaluations) evaluated the effects of irbesartan on morbidity and/or mortality in patients with hypertension and type 2 diabetes across the continuum of early and advanced stages of diabetic renal disease.

RENAAL study

Looking at these trials in detail, RENAAL randomised 1,513 patients with type 2 diabetes and signs of kidney function, with proteinuria and elevated serum creatinine, to losartan (50 mg o.d.) or placebo. The dose of losartan was titrated to 100 mg o.d. after four weeks if the target BP (140/90 mmHg) was not achieved. All patients had proteinuria (urinary albumin/creatinine 25 mg/mmol 24-hour urine protein > 500 mg, serum creatinine 133–265 mmol/L) and most (94%) had hypertension and were taking antihypertensives at the start of the study. They were all treated with conventional therapy including diuretics, vasodilators and/or beta blockers to achieve a target blood pressure below 140/90 mmHg. Treatment with ACE inhibitors or other AIIRAs was not allowed. All patients were followed for a mean of 3.4 years.

Results from RENAAL showed that patients taking losartan plus conventional antihypertensive therapy had a significant 16% reduction in the risk of the primary composite end point (p=0.024), which was a composite measure comprising time to the first occurrence of doubling of serum creatinine, end-stage renal disease, or death. This renal protective effect of losartan was found to exceed that attributable to any small differences in BP lowering. Further results showed that losartan significantly reduced the risk of progression to end-stage renal disease requiring dialysis or kidney transplantation by 28% (p=0.002). This and PRIME, were the first studies in which drug treatment has demonstrated a slowing of the progression to end-stage renal disease. The AIIRA also significantly reduced the risk of doubling of serum creatinine by 26% (p=0.006). Changes in proteinuria were also assessed in the RENAAL study. Results demonstrated that treatment with losartan plus conventional antihypertensives significantly reduced proteinuria by 35% compared to placebo plus standard treatment (p=0.0001).

The study also examined the effects of losartan on cardiovascular events. Results showed similar effects for both treatment groups for the composite end point of cardiovascular disease and death. But, importantly, hospitalisation for heart failure – a component of the cardiovascular composite end point – was significantly reduced by 32% (p=0.005) in patients randomised to losartan. A smaller number – 11.9% – of patients in the losartan group were hospitalised for heart failure compared to 16.7% of patients in the placebo group.

PRIME study

PRIME consisted of two trials:

- IRMA-2 (study of the effects of IRbesartan on MicroAlbuminuria in hypertensive patients with type 2 diabetes).
- IDNT (the Irbesartan Diabetic Nephropathy Trial).

IRMA-2 showed a significant reduction in the time to onset of diabetic nephropathy with irbesartan (300 mg daily) in patients with type 2 diabetes and hypertension who showed persistent low-grade proteinuria. IDNT demonstrated a 20% reduction in the risk of developing a doubling of baseline serum creatinine, development of end-stage renal disease or death from any cause in type 2 diabetic patients with hypertension and nephropathy compared to placebo (p=0.02).

IDNT included 1,715 type 2 diabetics with high blood pressure and proteinuria (defined as the presence of urinary protein excretion of at least 900 mg/day and serum creatinine levels of 110–265 µmol/L in men and 90–265 µmol/L in women). Patients were ran-

Key messages

- Hypertension is common in type 2 diabetics
- It is associated with increased risk of cardiovascular disease and deterioration in renal function
- Blood pressure should be tightly controlled
- Lifestyle changes and antihypertensive therapy should help achieve blood pressure targets
- Type 2 diabetes should be routinely monitored

domised to one of three arms: 300 mg/day irbesartan, 10 mg/day of the calcium channel blocker amlodipine, or placebo, in addition to antihypertensive therapy not including angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers or other AIIRAs. The primary composite end point was the time to a doubling of the baseline serum creatinine concentration (a measure that approximates to a halving of the glomerular filtration rate), the development of end-stage renal disease or death from any cause.

After a mean follow-up of 2.6 years, results from IDNT demonstrated that irbesartan reduced the progression of kidney disease and death rate by one fifth (20%) compared to placebo (p=0.02) and by one quarter (23%) compared to amlodipine (p=0.006). Treatment with the AIIRA reduced the relative risk of end-stage renal disease by 23% compared to placebo or amlodipine (p=0.07 for both comparisons). The researchers concluded that irbesartan was renoprotective in patients with type 2 diabetes and overt nephropathy and that it significantly slowed the progression of glomerulopathy.[9] IDNT showed no significant difference in a secondary cardiovascular end point – a composite of death from cardiovascular causes, non-fatal MI, heart failure hospitalisation, permanent neurological deficit after CVA or amputation due to peripheral arterial disease. This finding is consistent with other major morbidity and mortality trials directly comparing different classes of antihypertensive agents. As a secondary end point, the study was not powered to detect treatment group differences.

Both RENAAL and IDNT investigated the effects of AIIRAs in patients with proteinuria. In contrast, the IRMA-2 trial tested the effects of irbesartan in patients with persistent low-grade proteinuria, in addition to type 2 diabetes and hypertension. The trial randomised 590 patients with type 2 diabetes, high blood pressure and early signs of microalbuminuria (urinary albumin excretion rate [UAER] of 20–200 mcg/min) to irbesartan (150 mg or 300 mg once daily) or to placebo, in addition to other antihypertensive medications, excluding other AIIRAs or ACE inhibitors. The primary end point was the time to onset of diabetic nephropathy, defined by persistent albuminuria in overnight specimens with a UAER > 200 µg/min and an increase of more than 30% from baseline.

'Angiotensin II receptor antagonists protect renal function in patients with type 2 diabetes'

Results after two years of follow-up showed that the higher dose of irbesartan reduced the number of patients reaching the clinical end point of overt albuminuria by nearly three-quarters (70%) over 21 months compared to the control group (5.2% *vs.* 14.9%; p=0.0004). The restoration of normoalbuminuria by the last visit of the trial was significantly higher in patients treated with irbesartan (300 mg daily), with 34% achieving this secondary end point compared to 21% of the placebo group (p=0.006). The researchers suggested that the results showed that irbesartan significantly reduced the rate of progression to clinical albuminuria – the hallmark of overt diabetic nephropathy in patients with type 2 diabetes.[10]

Added benefits of AIIRAs

In addition to a renoprotective effect, there are several practical benefits with AIIRAs, both in terms of efficacy in lowering blood pressure and in tolerability. These agents are highly effective in lowering blood pressure, blocking the AT_1 receptor and preventing angiotensin II from binding to the receptor site. They do this more effectively than ACE inhibitors as they block angiotensin formed through non-ACE as well as ACE pathways.

Side effects with other classes of antihypertensives are a common reason for patients failing to comply with treatment. This is a major problem in achieving effective management of hypertension, which relies on good, long-term compliance with treatment. A UK study showed that over half of patients on traditional antihypertensives – including diuretics, calcium channel blockers, ACE inhibitors and beta blockers – discontinued their medication after six months.[11] In contrast, a major follow-up study with the AIIRA, losartan, demonstrated that up to twice as many patients continued treatment as with other classes of antihypertensive.[12] Results from the RENAAL study confirmed that losartan had excellent tolerability. Slightly fewer patients treated with losartan discontinued the study due to clinical adverse events compared to the placebo group (17% *vs.* 22%). In the IRMA-2 study, serious adverse events were more common in the placebo group, occurring in 22.8% of patients, compared to 15.4% in patients taking irbesartan (150 mg or 300 mg daily). Non-fatal cardiovascular events were slightly, but not significantly, more frequent in the placebo group.

One of the main advantages is that the AIIRAs are not associated with some of the side effects caused by other groups of antihypertensives, such as the irritating cough that can occur with ACE inhibitors, flushing with calcium channel blockers and impotence with beta blockers.

Implementing the guidelines in practice

How can practices and Primary Care Organisations (PCOs) best act on available guidelines in order to improve the management of hypertension in patients with diabetes and offer them optimal care? The first step is to ensure that practices are using appropriate protocols to manage all aspects of diabetes, including hypertension. Most practices will now be auditing their care of patients with diabetes as part of clinical governance measures, making systematic management easier to achieve and monitor. Recording data on an agreed template ensures that all important questions are asked and all important measures are taken – or at least discussed – with the patient. In addition, the template shows whether or not a criterion (such as achieving target blood pressure) has been achieved.

Patients with diabetes should have their blood pressure measured, recorded and monitored on a regular basis. Those with blood pressures above the recommended targets should be treated aggressively – with lifestyle advice, including recommendations to achieve the right weight for their height and to take regular physical activity, and drug treatment. Type 2 diabetics should have their urine tested every year for microalbuminuria as part of their routine monitoring, in addition to other checks. Anyone who tests positive should be treated aggressively – with tight control of their diabetes in addition to reduction of blood pressure to target level. The new studies tell us that all hypertensive patients with type 2 diabetes would benefit from treatment with an AIIRA with regards to both their renal function and their BP.

The guidelines recommend certain drug choices in the management of hypertension in diabetics but recent research evidence indicates that type 2 diabetic patients with any degree of renal disease should be treated with an AIIRA. The SIGN guidelines point out that thiazides, beta blockers, ACE inhibitors and calcium channel blockers are all effective in lowering blood pressure and reducing the risk of cardiovascular events. They suggest that ACE inhibitors should be considered as first-line therapy in patients with microalbuminuria due to their additional benefit on renal function; AIIRAs are recommended as alternatives in patients with ACE inhibitor-induced cough or rash.

The next step in improving the management of diabetic hypertension is to use these protocols within suitable frameworks for care. Many practices and PCOs have found that diabetes clinics provide a useful way of managing diabetes in a cohesive and organised manner. To run efficiently, clinics should ideally be run by specialist doctors and/or nurses in diabetes. Better funding provision for nursing staff is required to enable practices to develop diabetes clinics further.

Conclusion

It is important to stop deterioration of kidney function in people with diabetes and, if possible, reverse it to as near normality as possible. We are already facing an epidemic of type 2 diabetes with incidence steadily increasing. We don't have enough donor kidneys or dialysis facilities to treat all patients who progress to kidney failure, so this is another good reason to protect the kidneys in diabetics. We now have clear evidence that AIIRAs, such as losartan and irbesartan, offer not only blood pressure reduction for patients with diabetes and hypertension but also protect their kidneys from damage, independent of their effect on blood pressure. These drugs slow the progression of kidney disease and delay or prevent the need for dialysis or transplantation. Dialysis has a major adverse impact on a patient's quality of life; avoiding – or delaying – deterioration of kidney function to this stage is an essential aim of management. It is up to us to ensure that AIIRAs are used to full effect as part of providing the best possible care we can achieve for the growing number of our patients who have diabetes.

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References

1. United Kingdom Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**:703-13.
2. National Service Framework for Diabetes. Website: www.doh.gov.uk/nsf/diabetes
3. Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes: a national clinical guideline. Edinburgh: SIGN, 2001 (SIGN publication no.55). Website: www.sign.ac.uk.
4. Ansell D, Feest T (eds). United Kingdom Renal Registry, Bristol, December 1999.
5. Ritz E, Reinhold S. Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 1999;**341**:1127-33.
6. Parving HH. Renoprotective action of angiotensin-converting enzyme inhibition in diabetes mellitus. *J Cardiovasc Pharmacol* 1992;**19**(suppl 6):S19-24.
7. Collin R, McMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull* 1994;**50**:272-98.
8. Ramsay LE, Williams B, Johnstone DG *et al*. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *J Hum Hypertens* 1999; **13**:569-92.
9. Lewis EJ, Hunskicker LG, Clarke WR *et al*. Renoprotective effect of the angiotensin receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *JAMA* 2001;**345**:851-60.
10. Parving HH, 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**:870-8.
11. Jones JK, Gorkin L, Lian JF *et al*. Discontinuation of and changes in treatment after start of new courses of antihypertensive drugs: a study of a United Kingdom population. *BMJ* 1995;**311**: 293-5.
12. Mann RD, Mackay F, Pearce G *et al*. Losartan: a study of pharmacovigilance data on 14,522 patients. *J Hum Hypertens* 1999;**13**:551-7.