

Backgrounder

Diabetes and hypertension

Notes to editors

There is a well-established relationship between diabetes and hypertension and people with diabetes are especially vulnerable to blood pressure-mediated macrovascular and microvascular damage. Numerous studies, including the United Kingdom Prospective Diabetes Study (UKPDS), show that aggressive blood pressure lowering in patients with diabetes is more effective at reducing cardiovascular risk when compared with the non-diabetic population. There is also evidence from recent studies, such as the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), that certain antihypertensive drug classes may be more effective than others in preventing new-onset diabetes and atherosclerotic complications. Patients with diabetes will require multiple antihypertensive therapies in order to meet lower blood pressure targets.

This backgrounder provides further details on:

- *The relationship between hypertension and diabetes*
- *The benefits of treating hypertension in diabetic patients*
- *The differences between antihypertensive therapies in diabetic patients*
- *Treatment guidelines in diabetic patients with hypertension*

What is the association between diabetes and hypertension?

It has been well-recognised for over 20 years that type 2 diabetes and hypertension are closely linked. The following few statistics show the close and complex relationship between diabetes, high blood pressure (BP) and cardiovascular disease:

- Hypertension is much more common in type 2 diabetes than in the general population. Nearly 40% of patients recruited for the United Kingdom Prospective Diabetes Study (UKPDS) with newly diagnosed type 2 diabetes were hypertensive.¹
- The worldwide prevalence of diabetes is projected to exceed 300 million by 2025 and 75 percent of these patients are likely to die from cardiovascular disease.²
- The risk of any cardiovascular event is 2-4 times greater in patients with diabetes than in non-diabetics.³
- Hypertension in diabetic patients is associated with accelerated development of macrovascular and microvascular disease.⁴

What are the benefits of treating hypertension in diabetes?

The UKPDS and analyses of diabetic sub-groups from many studies in the treatment of hypertension have shown that people with diabetes benefit more from BP reduction than non-diabetic patients. Significant improvements have been seen in macrovascular endpoints such as myocardial infarction and stroke when hypertension is carefully managed in patients with diabetes.⁵

The UKPDS investigated the effects of glycaemic control in patients with type 2 diabetes.⁶ About 40 percent of these patients were hypertensive with a systolic BP ≥ 160 and/or diastolic BP ≥ 90 mmHg. Tight BP control with a mean achieved blood pressure of 144/82 resulted in a 44 percent reduction in stroke and 32 percent reduction in deaths related to diabetes (mainly myocardial infarction and stroke) compared with a less tight BP reduction of 154/87 mmHg. The UKPDS also showed that treatment of

hypertension in patients with diabetes was associated with reduction in microvascular endpoints.

Other studies have shown that the greater the BP lowering the greater the benefit in terms of cardiovascular events, and there appears to be no BP threshold below which risk no longer declines.⁷ Strict control of hypertension in diabetics has been shown to be one of the most important factors in preventing the development of diabetic nephropathy and end stage renal failure.⁸

A number of randomised trials (including ALLHAT, RENAAL, BENEDICT, HOT, Syst-Eur) have highlighted the benefits of using a variety of antihypertensive therapies in people with diabetes. These studies in diabetes and hypertension firmly establish antihypertensive therapy as the foundation for microvascular and macrovascular disease protection in people with diabetes.

Are there differences between antihypertensive therapies in treating diabetic patients?

Diabetes is now considered a 'coronary heart disease risk-equivalent' meaning that it contributes as much to the coronary event risk profile as does a previous history of a coronary event. A recent study shows that patients with diabetes fall into the high risk category for cardiovascular disease 15 years earlier than those without diabetes.⁹ It is therefore vital to control blood pressure in patients with diabetes. Numerous guidelines stress the need for lower blood pressure targets for patients with diabetes.

In clinical practice, a high proportion of patients with diabetes require three or more antihypertensive agents to achieve adequate blood pressure control. Moreover, there is evidence from some studies such as ASCOT-BPLA that the type of treatment regimen used to control blood pressure influences the clinical outcome of patients with diabetes and hypertension.

Restricting the progression of renal disease has been suggested as being important in preventing cardiovascular disease in patients with diabetes, although it has not been shown to prevent cardiovascular events. Studies of patients with diabetic renal disease, such as microalbuminuria or proteinuria, show that effective blockade of the renin-angiotensin system reduces albumin excretion more effectively than equivalent BP-lowering with other drugs. Several studies now provide strong evidence for the importance of renin-angiotensin blockade in nephroprotection and reduction in surrogate markers such as proteinuria.¹⁰ Both angiotensin II receptor antagonists and ACE inhibitors have been shown to reduce albuminuria, and angiotensin II receptor antagonists have been shown to delay the progression of established renal disease towards end-stage renal failure in type 2 diabetes. However it should be remembered that patients with diabetic nephropathy comprise a minority of patients with diabetes and ACE inhibition has not been demonstrated to have a beneficial effect on cardiovascular outcome compared with other treatments. Blood pressure reduction is the main strategy of better cardiovascular outcomes and will require more than one drug class to achieve appropriate targets.

It is now well accepted that management of blood pressure, lipids and smoking is just as important as controlling blood glucose in people with diabetes. Smoking cessation is likely to yield significant benefits in a population at such high risk of cardiovascular events. Effective care in diabetes requires a team approach working across all healthcare boundaries.

What is the impact of antihypertensive therapy on the onset of diabetes?

Prospective data from large-scale cohort studies and randomised trials indicate that thiazide and other diuretics and beta-blockers are associated with an increased risk of developing type 2 diabetes in men and women with a history of hypertension.^{11,12,13} There is evidence that diuretics, particularly in association with beta-blockers, are diabetogenic – in that they amplify the time-dependent tendency towards the

development of diabetes in all subjects and particularly in those who are at a higher risk or predisposed individuals.¹⁴ Some authors have suggested that these effects with these older drugs may be due, at least in part, to reduced blood flow to the skeletal muscle tissue which increases the distance insulin has to travel to allow entrance of glucose into cells, therefore reducing insulin sensitivity.¹³ The potassium-lowering effects of many diuretics may also be responsible for reducing insulin sensitivity. In contrast, recent findings from the ASCOT-BPLA study show that patients allocated the amlodipine-based regimen were 31 percent less likely to develop diabetes compared to those allocated the atenolol-based regimen.¹⁵

What do recent guidelines recommend for the treatment of hypertension in diabetes?

Most hypertension guidelines now stress the importance of blood pressure reduction in patients with diabetes with lower treatment targets for these patients. Multiple antihypertensive therapies are required to achieve these lower targets.

The NICE guidelines and British Hypertension Society IV (BHS IV) guidelines from 2004 have recently been updated and amalgamated following the results of major trials such as ASCOT. This new combined guideline presents a single national treatment algorithm for hypertension.¹⁶

The new BHS IV algorithm reflects the latest data showing that calcium channel blockers and thiazide diuretics are the most effective initial therapy for hypertension among those aged ≥ 55 years or in patients of African origin of any age. Beta-blockers are no longer preferred as a routine initial therapy for hypertension as they are proven to be less effective at preventing cardiovascular events, particularly strokes, than other treatments. However, the guidelines state that if a patient taking a beta-blocker requires a second drug, a calcium channel blocker should be added rather than a thiazide diuretic, to reduce the patient's risk of developing diabetes.

The 2002 NICE guidelines on the treatment of diabetes recommend that pharmacological treatment is started when blood pressure is >140/80 mmHg.¹⁷ The NICE guidelines are currently being revised and will be published in 2008.

The BHS IV hypertension guidelines from 2004 recommend a blood pressure target of ≤130/80 mmHg for patients with diabetes.¹⁸ These recommendations are based on results from the HOT trial which, although underpowered, are the best available at the moment.

Most guidelines, for example ESC, ESH and JNC VII, recommend treatment with antihypertensive therapy at blood pressure thresholds of ≥140/90 mmHg for people with diabetes, with lower intervention thresholds of 130/80 for people with target organ damage. Although optimal blood pressure targets have been poorly defined, a general principle of 'lower is better' has been adopted and a target of <130/80 mmHg is commonly advocated by guidelines. These guidelines agree that patients with diabetes and hypertension should be treated aggressively with combination antihypertensive therapy as soon as possible.

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