Rev Bras Hipertens vol.13(1): 8-13, 2006.

The management of hypertension in type II diabetes mellitus

Jawad M Khan[1], Gregory YH Lip[1]

ABSTRACT

The prevalence of both hypertension and type II diabetes mellitus are increasing in industrialised countries. These diseases are very closely related and associated with a high incidence of cardiovascular, cerebrovascular and renovascular complications.

Effective management of hypertension in type II diabetes reduces the associated morbidity and mortality. The target blood pressure in patients with type II diabetes mellitus is less than 130/80 mm Hg, with a lower level of less than 120/80 mm Hg being recommended in the context of renal impairment or proteinuria. All groups of antihypertensive drugs are effective in reducing hypertension in diabetics with the individual agent, or combination of agents, used dictated by patient characteristics, including age and ethnicity, in addition to co-morbidities. Often, an ACE inhibitor or an angiotensin II receptor blocker, usually combined with a diuretic, would be first line therapy. A calcium-channel blocker, beta-blocker, or alpha-blocker may be used as additional therapy if required.

KEY WORDS

Hypertension, diabetes mellitus, cardiovascular disease, pathophysiology, renoprotection.

INTRODUCTION

The increase in obesity has led to a rapid rise in the incidence of type II diabetes in industrially developed countries. More than 300 million people worldwide have type II diabetes[1] with more than 20 million in the United States of America[2]. The epidemic of type II diabetes is no more pronounced than in the non Caucasian population in the developing countries and among minority groups in the industrial world.

In a Western adult population the prevalence of hypertension exceeds 20%[3]. This prevalence increases with age and is higher in ethnic minority groups in the UK. In the Health Survey for England (2001), the prevalence of hypertension was 3.3% in those aged <40 years, 27.9% in those aged between 40 and 79 years, and 49.9% in those aged 80 years and older[4].

All too often, hypertension and type II diabetes are managed as distinct clinical entities. However, they are both very closely inter-related diseases. Indeed, hypertension affects 20-60% of people with type II diabetes and people with hypertension are more than twice as likely to develop type II diabetes[5]. The prevalence of hypertension in the diabetic population is 1.5–3 times higher than that of non diabetic age-matched groups[6].

Importantly, each condition is a risk factor for cardiovascular disease, however, together they strongly predispose to end-stage renal failure, coronary artery disease, peripheral artery disease and cerebrovascular disease. Serious cardiovascular events are more than twice as likely in patients with both diabetes and hypertension, than in patients with either condition alone[8].

Recebido: 15/12/2005 Aceito: 05/01/2006

1 University Department of Medicine, City Hospital. Birmingham, England

Correspondence to: Gregory YH Lip. Consultant Cardiologist and Professor of Cardiovascular Medicine, Director - Haemostasis Thrombosis & Vascular Biology Unit, Editor - Journal of Human Hypertension, University Department of Medicine , City Hospital, Birmingham B18 7QH, England UK. Tel: +44 121 5075080; Fax: +44 121 554 4083; e-mail: g.y.h.lip@bham.ac.uk

The objective of this review article is to discuss the importance of hypertension in type II diabetes mellitus, as well as management implications.

PATHOPHYSIOLOGY – A BRIEF OVERVIEW

Although obesity is a common link between the two disorders, resistance to insulin mediated glucose uptake and vascular endothelial dysfunction are also involved[9]. Excess weight with truncal obesity, hypertension, insulin resistance with impaired glucose tolerance and dyslipidaemia, comprise the metabolic syndrome, giving an increased risk of cardiovascular disease[10].

Insulin utilises similar post-receptor signalling mechanisms in regulating nitric oxide synthesis to those used in promoting glucose uptake in target tissues, such as muscle and fat. Therefore, inherited or acquired defects in insulin signalling may have parallel effects on insulin sensitivity and endothelial function. Equally, adipocyte derived factors have parallel effects on insulin signalling in classical insulin target tissues and in the vasculature[5].

The glomerulus is an anatomically unique structure, with an afferent arteriole at the front of the glomerulus and an efferent arteriole at its back. Together, they regulate pressure within the glomerulus, which is normally approximately half that of systemic blood pressure. The afferent arteriole constricts when systemic pressure is too high, reducing the pressure of the blood entering the glomerulus. Conversely, when it is too low, angiotensin II constricts the efferent glomerular arteriole restoring glomerular capillary pressure[11].

This microcirculation responds almost instantly to systemic pressure changes, and by doing so, the pressure within the glomerulus is kept relatively constant across a wide range of systemic pressures. Even in early diabetes, the afferent arteriole's ability to constrict in response to increased systemic pressure is impaired. Therefore, the increased afferent pressure is transmitted to the glomerulus, resulting in progressive kidney damage. In addition, the efferent glomerular arteriole is more sensitive to the vasoconstrictive action of angiotensin II. The resultant kidney damage exacerbates the already elevated blood pressure, which in turn produces further kidney damage[11].

In summary, the pathophysiology of both type II diabetes mellitus and hypertension are closely linked, with parallel progression of both conditions, resulting in potentiation of risk and acceleration of end organ damage.

WHAT IS THE IDEAL BLOOD PRESSURE FOR DIABETIC HYPERTENSIVE PATIENTS? A BRIEF OVERVIEW OF RECENT TRIAL DATA

The Hypertension Optimal Treatment (HOT) study[12] investigated the effect of intensive blood pressure lowering in 19,193 patients with hypertension and diastolic pressures between 100 and 115 mm Hg, where 8% (n=1501) of patients had type II diabetes. The patients were randomly assigned to one of three target diastolic blood pressure groups: less than 90 mm Hg, less than 85 mm Hg, or less than 80 mm Hg. There was a 51% reduction in major cardiovascular events and 43% reduction in cardiovascular mortality in diabetic patients who were randomly assigned to a target diastolic blood pressure group with a goal at or below 80 mm Hg. The mean diastolic pressure was 81.1 mm Hg in those patients assigned to the 'less than 80 mm Hg' group and 85.2 mm Hg in those assigned to the 'less than 90 mm Hg' group. Despite this relatively small difference in achieved pressure, there were significant reductions in all major events (coronary disease, 60%; stroke, 43%; and mortality, 77%)[12].

The UK Prospective Diabetes Study (UKPDS) involved 1,148 hypertensive patients (mean blood pressure, 160/94 mm Hg) with type 2 diabetes[13]. In this study, 66% of patients were assigned to tight control of blood pressure (<150/85) and 34% of the patients to 'less tight' blood pressure control (<180/105). Median follow up was 8.4 years, with blood pressure in the 'tight control' group being reduced to 144/82 mm Hg and 154/87 in the 'less tight' group. 'Tight control' was associated with a 24% reduction in diabetes-related end points, 32% in deaths related to diabetes, and 37% in microvascular end points (nephropathy and advanced retinopathy). There was a 29% reduction in the risk of developing urinary albumin levels >50 mg/l at 6 years in the 'tight control' group with no significant changes in the development of overt proteinuria or increase in plasma creatinine levels between the two groups[13]. Similarly, the Appropriate Blood Pressure Control in Diabetes (ABCD) study showed a 51% reduction in all-cause mortality among patients who received more intensive therapy[14].

Reduction of systolic blood pressure in diabetic patients with isolated systolic hypertension (systolic more than or equal to 160 mm Hg, diastolic less than or equal to 90 mm Hg) reduced relative and absolute risk of nonfatal and fatal cardiovascular events (both coronary and cerebral) in diabetic as well as non-diabetic patients. The benefit seen in diabetic patients was even greater[15].

In view of these data, the American Diabetes Association (ADA) and National Kidney Foundation (NKF) currently recommend blood pressure to be decreased to less than 130/80 mm Hg in type II diabetes, with an optimal target of below 120/80 mm Hg, especially in patients with proteinuria or renal insufficiency[16,17]. The Sixth Joint Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI) classifies optimal blood pressure for cardiovascular risk to be at or below 120/80 mm Hg in adults aged 18 years or older; 'normal' blood pressure is classified as at or below 130/85 mm Hg[18].

MANAGEMENT OF THE HYPERTENSIVE DIABETIC PATIENT

Effective management of hypertension in diabetics significantly reduces cardiovascular risk. Clearly, management of hypertension should be part of the holistic approach to the treatment of patients with diabetes mellitus.

In the Systolic Hypertension in the Elderly Program (SHEP)[19] the absolute risk reduction was twofold greater in diabetic patients (n=583) compared to the non-diabetics (n=4149). Similarly, the adjusted relative hazards for all cardiovascular events in the Systolic Hypertension in Europe Trial (Syst-Eur) trial[20] were reduced by 69% in the diabetic patients (n=492) and 26% in the non-diabetics (n=4203). Of note, more intensive control of hypertension (diastolic blood pressure of 87mmhg vs. 82mmHg) resulted in a two to five fold absolute risk reduction, when compared to intensive glucose control (mean haemoglobin A_{1C} level 7.9% vs. 7.0%)[13,21]. This emphasises the even greater need for appropriate blood pressure management in such diabetic patients.

NON-PHARMACOLOGICAL MANAGEMENT

Diet has an important role in the management of both hypertension and diabetes. Reduction of sodium salt intake with the use of unprocessed and fresh foods, with an increase in potassium salt, has been shown to decrease blood pressure[22]. In diabetic patients, excessive sodium salt reduces the beneficial effects of anti hypertensives on proteinuria[23]. An increase in exercise with reduction of weight also improves insulin resistance and glycaemic control, in addition to lowering blood pressure[24].

Moderately intense physical activity, such as 30–45 mins of brisk walking most days of the week, smoking cessation and moderation of alcohol intake are associated with a reduction of blood pressure and is currently recommended by the JNC VI as part of the overall management strategy to reduce blood pressure[25-27].

PHARMACOLOGICAL MANAGEMENT

An ACE inhibitor or an angiotensin II receptor blocker are usually the first line agents in the treatment of hypertension in type II diabetes, usually with the addition of a diuretic. If additional therapy is needed, a calcium-channel blocker, beta-blocker, or alpha-blocker may be used.

(A) Angiotensin Converting Enzyme Inhibitors (ACEinhibitors)

ACEinhibitors are considered to be the preferred therapy in patients with hypertension and diabetes, according to the main guidelines from the ADA, the NKF, and JNC VI[16-18]. In hypertension, ACE inhibitor therapy results in a 20-30% decrease in the risk of stroke, coronary heart disease, and major cardiovascular events[29]. Diabetic patients may have impaired fibrinolysis and endothelial dysfunction, which increases their risk of cardiovascular disease; importantly, ACE inhibitors have been shown to improve fibrinolysis and endothelial dysfunction[30,31]. ACE inhibitors have also been shown to increase insulin sensitivity[9].

In the Heart Outcomes Prevention Evaluation (HOPE) study, the ACEinhibitor, ramipril was given to half of the 'high-risk' population (diabetes with one additional cardiovascular risk factor in patients older than 55 years of age). The study included approximately 3600 diabetic patients and 5300 hypertensive patients, most of who were being treated with other antihypertensive agents. The study was not a trial of antihypertensive therapy *per se*, and no attempt was made to reach a predetermined level of blood pressure. Blood pressure was lower by only 2/1 mm Hg in patients who received an ACEinhibitor compared with those who received placebo. Despite this, there was a combined reduction in myocardial infarction, cardiovascular death and stroke at 5 years of 22 % and a 17% reduction in all cause mortality in the ramipril treatment group[32].

In the Captopril Prevention Project (CAPPP) trial, patients with hypertension were randomly assigned to captopril or treatment with ß-blockers or diuretics; target diastolic blood pressure was less than 90 mm Hg[33]. In the 572 patients with diabetes blood pressure control was similar. However, in the captopril group, risk for all-cause mortality, cardiovascular events, and myocardial infarction was lower (RR, 0.34 [CI, 0.17 to 0.67]).

(B) Angiotensin II Receptor Blockers (ARBs)

Losartan, irbesartan, telmisartan, candesartan, eprosartan, and valsartan are effective antihypertensive agents[34,35]. Patients with type 2 diabetes, hypertension, and microalbuminuria were studied in the Candesartan and Lisinopril Microalbuminuria (CALM) study. Results showed that candesartan was as effective as lisinopril in blood pressure reduction and minimization of microalbuminuria[36].

In the Reduction of Endpoints in Non Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study, losartan therapy produced a renoprotective effect, independent of its blood-pressure lowering effect in patients with type 2 diabetes and nephropathy[37]. Angiotensin receptor blockers also have been shown to retard the progression of albuminuria and the development and progression of nephropathy. Angiotensin II receptor blockers have been shown to decrease proteinuria[38,39].

(C) Thiazide diuretics

In the Systolic Hypertension in the Elderly Program (SHEP) trial, low-dose chlorthalidone (12.5 to 25mg) therapy was effective in preventing major cerebrovascular and cardiovascular events in older non-insulin treated patients with diabetes and isolated systolic hypertension[19].

Lower dosages of thiazides (e.g., hydrochlorothiazide, 12.5 mg per day) are generally well tolerated and not associated with adverse metabolic effects[15]. At these doses thiazides do not appear to increase the risk of diabetes.[40] Moreover, diuretics will probably often be needed to achieve goals of therapy because they enhance the efficacy of most other classes of antihypertensive drugs and because volume retention is a common feature of hypertension in diabetic patients. Thiazide diuretics are not as effective in patients with renal insufficiency; in such patients, loop diuretics are preferred. In general, diuretics are pretty effective in the treatment of hypertension[9].

(d) Calcium Channel Blockers (CCBs)

The use of dihydropyridine CCBs, as monotherapy or in combination with another agent, was associated with a reduction in cardiovascular risk in the Hypertension Optimal Treatment (HOT) trial[12], the Systolic Hypertension in Europe (Syst-Eur) trial[20], and the Isolated Systolic Hypertension in China study[41]. The combination of an ACE inhibitor and a dihydropyridine CCB has been shown to significantly reduce proteinuria[42].

Diltiazem, a non dihydropyridine CCB, was compared with ß-blocker/diuretic–based treatment in the Nordic Diltiazem Trial[43]. There was a significantly lower risk of stroke for patients treated with diltiazem-based therapy compared with the ß-blocker/diuretic–therapy group, but a non significant trend toward higher rates of myocardial infarction, cardiovascular death, and congestive heart failure in the diltiazem group. No differences in combined cardiovascular events or mortality were seen, with no difference in results between diabetic and non-diabetic patients.

(e) Beta blockers

Traditionally, the use of beta blockers in patients with diabetes has been discouraged because of adverse worsening of glucose tolerance and insulin sensitivity[40], However, in the UKPDS[13], a beta-blocker was more protective than an ACE inhibitor suggesting that the benefits of this class outweigh its potential harm. As diabetic patients with hypertension are at high risk for coronary disease, beta-blockers are more likely to be beneficial.

Cardioselective beta-blockers, such as bisoprolol or metoprolol, are associated with less blunting of hypoglycemic awareness, and less elevation of lipid and glucose levels, and are therefore preferred to non-selective agents. Carvedilol, a combined alpha$_1$ beta-blocker, has been shown to cause fewer alterations in lipid and glucose levels compared with traditional beta-blockers in diabetics[44]. Also, beta-blockers have proven ability to decrease cardiovascular morbidity and mortality in persons with atherosclerotic heart disease[45].

In summary, all groups of antihypertensive drugs cause reduction of blood pressure in diabetics and are beneficial in reducing cardiovascular morbidity and mortality. The individual agent, or combination, used will be dictated by patient characteristics, including age and ethnicity, in addition to co-morbidity.

COMPARATIVE STUDIES

More than one antihypertensive will normally be required to achieve target blood pressure in type II diabetic patients. On average, half will require two drugs and a third will require three or more drugs. The use of monotherapy to achieve adequate blood pressure control is unusual.

In the Hypertension Optimal Treatment (HOT) trial[12], for example, 68% of patients were maintained on combination antihypertensive therapy (usually felodipine, with an ACE inhibitor, beta blocker and/or a diuretic) to achieve targeted level of blood pressure. The Swedish Trial of Old Patients with Hypertension-2 (STOP-2) trial compared drugs from the three major classes of antihypertensive agent: calcium-channel blockers, ACE inhibitors, and beta-blockers plus diuretics. It included 6614 elderly hypertensive patients, 719 of whom had diabetes mellitus. Patients who received an ACE inhibitor had lower rates of coronary disease and heart failure; however, rates of stroke and mortality were lower in those who received a dihydropyridine calcium-channel blocker[46].

The Irbesartan Diabetic Nephropathy Trial (IDNT) randomly assigned 1715 patients with diabetes, hypertension, and nephropathy into three groups: irbesartan, amlodipine, and placebo[47]. Irbesartan was more effective than amlodipine or placebo in preventing the primary end point of doubling of serum creatinine concentration, development of end-stage renal disease, or death.

The Losartan Intervention for Endpoint Reduction (LIFE) study randomly assigned patients with hypertension and signs of left ventricular hypertrophy on electrocardiography to an angiotensin II receptor blocker (losartan) or a beta-blocker (atenolol) [48]. In a prespecified subgroup analysis of 1195 patients with diabetes mellitus, the losartan group had a substantially lower risk for cardiovascular end points and total mortality. The risk for microalbuminuria was also lower in the losartan group

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) compared ACE inhibitors, calcium-channel blockers, and thiazide diuretics[49]. Blood pressure control was slightly (but significantly) different between the groups - systolic blood pressure was best in the diuretic group, while diastolic blood pressure was best in the calcium-channel blocker group. In the 12063 patients with type II diabetes, no significant differences were seen between the groups in the primary outcomes of nonfatal myocardial infarction plus coronary heart disease, death or all-cause mortality.

In the Captopril Prevention Project (CAPPP) trial, hypertensive patients were randomised to captopril or treatment with

beta-blockers or diuretics; target diastolic blood pressure was less than 90 mm Hg[33]. Blood pressure control was similar in the 572 patients with diabetes. However, risk for all-cause mortality, cardiovascular events, and myocardial infarction was lower in the captopril group.

In UKPDS, the intensive control group (target blood pressure $<$ 150/85 mm Hg) were randomised to atenolol or captopril[13]. Both groups achieved similar blood pressure. (143/81 mm Hg vs. 144/83 mm Hg).

In summary, trial data supports the use of most classes of antihypertensives in diabetic patients. Most patients require more than one agent to achieve target blood pressure levels. ACE inhibitors and ARBs are first line therapy due to their additional renoprotective and vascular endothelial effects. In addition to being effective antihypertensives, thiazide diuretics usually potentiate the effects of ACE inhibitors, ARBs and beta-blockers and are often used in combination. The presence of additional co-morbidity may alter preference for first line therapy, for example, beta-blockers in patients with coronary heart disease or alpha-receptor blockers in patients with concomitant benign prostatic hypertrophy and prostatism (Figure 1).

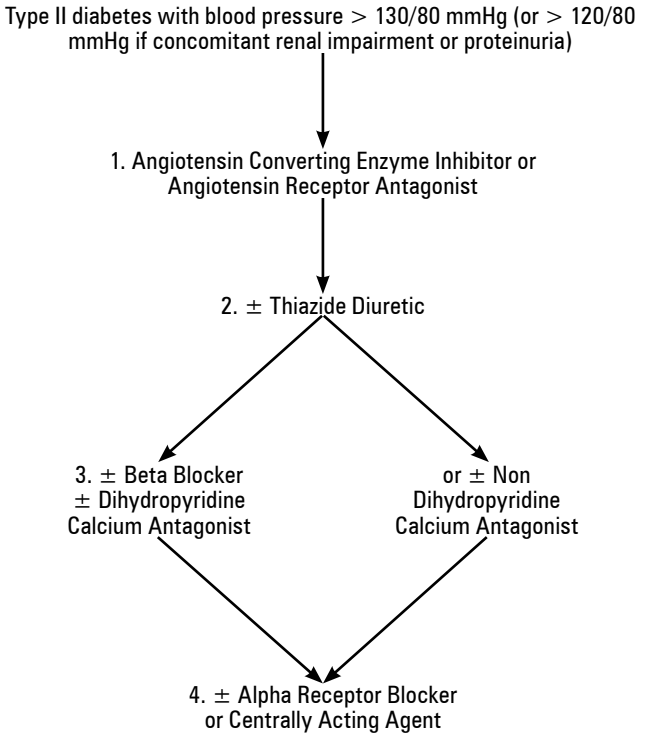

Figure 1. An algorithm for the treatment of hypertension in type II diabetes mellitus.

CONCLUSION

The incidence of type II diabetes and hypertension are increasing. Effective treatment of both reduces associated morbidity and mortality. An integrated approach to the management of hypertensive diabetics is needed, with attention to blood pressure, hyperglycaemia and other risk factors such as dyslipidaemia. Lifestyle changes should be emphasised such as weight reduction; regular exercise; smoking cessation and moderation of sodium and alcohol.

More than one antihypertensive drug will usually be required to achieve the target blood pressure, and an ACE inhibitor or an angiotensin II receptor blocker, usually combined with a diuretic, are used as first line therapy. A calcium-channel blocker, beta-blocker, or alpha-blocker may certainly be used (and are often required) as additional therapy to achieve blood pressure control.

REFERENCES

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414-31.
2. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS. Diabetes trends in the U.S.: 1990-1998. *Diabetes Care* 2000;23:1278-83.
3. Chapman N, Mayet J, Brady A. Hypertension: Special issues in different ethnic groups. New Perspectives in Hypertension. *Merit Publishing International* 2003:124-9.
4. Beevers DG, Lip GYH, O'Brien E. ABC of Hypertension, 4th Edn. London, *BMJ Publishing Group* 2001:12.
5. Petrie J. Mechanisms contributing to hypertension in type 2 diabetes. *Endocrine Abstracts* 2003;DS2.
6. Wingard DL, Barrett-Connor E. Heart disease and diabetes. In Diabetes in America. Washington, DC, U.S. Govt. *Printing Office* 1995:429-48.
7. Bakris G, Sowers J, Epstein M, Williams M. Hypertension in patients with diabetes. Why is aggressive treatment essential? *Postgraduate Medicine* 2000;2:107.
8. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434-44.
9. Fineberg SE. The treatment of hypertension and dyslipidemia in diabetes mellitus. *Prim Care* 1999;26:951-64.
10. Vega GL. Results of expert meetings: obesity and cardiovascular disease. Obesity, the metabolic syndrome, and cardiovascular disease. *Am Heart J* 2001;142:1108-1116.
11. Weir MR. Hypertension in Patients with Type 2 Diabetes. Hospital Practice. Decision making in Medicine 2001. http://www.hosppract.com/issues/2001/01/dmmweir.htm
12. Hansson L, Zanchetti A, Carruthers SG *et al.* Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998;351:1755-62.
13. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macro vascular and micro vascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998;317(7160):703-13.
14. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic micro vascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000;23(2):54-64.
15. Curb JD, Pressel SL, Cutler JA *et al.* Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;276(23):1886-92.
16. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002;25:213-29.
17. Bakris GL, Williams M, Dworkin L *et al.* for the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis* 2000;36:646-61.

18. National High Blood Pressure Education Program. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. November 1997.
19. Curb JD, Pressel SL, Cutler JA *et al.* Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996;276:1886-92.
20. Tuomilehto J, Rastenyte D, Birkenhäger WH *et al.* Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med* 1999;340:677-84.
21. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837-53.
22. Moore TJ, Conlin PR, Ard J, Svetkey LP. DASH (Dietary Approaches to Stop Hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. *Hypertension* 2001;38:155-8.
23. Bakris GL, Smith A. Effects of sodium intake on albumin excretion in patients with diabetic nephropathy treated with long-acting calcium antagonists. *Ann Intern Med* 1996;125:201-4.
24. Konzem SL, Devore VS, Bauer DW. Controlling Hypertension in Patients with Diabetes. *American Family Physician* October 1, 2002.
25. Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). *Arch Int Med* 1997;157:2413-446.
26. American Diabetes Association: Smoking and diabetes (Position Statement). Diabetes Care 2002;25:S80-1.
27. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes (Technical Review). *Diabetes Care* 1999;22:1887-9.
28. Kaplan NM. Management of Hypertension in Patients with Type 2 Diabetes Mellitus: Guidelines Based on Current Evidence. *Annals of Internal Medicine Dec* 2001;135:1079-83.
29. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000;356:1955-64.
30. Vaughan DE, Rouleau JL, Ridker PM, Arnold JM, Menapace FJ, Pfeffer MA. Effects of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction. HEART Study Investigators. *Circulation* 1997;96:442-7.
31. Di Pasquale P, Valdes L, Albano V *et al.* Early captopril treatment reduces plasma endothelin concentrations in the acute and subacute phases of myocardial infarction: a pilot study. *J Cardiovasc Pharmacol* 1997;29:202-8.
32. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and micro vascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253-9.
33. Hansson L, Lindholm LH, Niskanen L *et al.* Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999;353:611-6.
34. MacKay JH, Areuri KE, Goldberg AI, Snapinn SM, Sweet CS. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension: a double-blind, placebo-controlled trial of concomitant administration compared with individual components. *Arch Intern Med* 1996;156:278-85.
35. Ruilope LM, Simpson RL, Toh J, Arcuri KE, Goldberg AL, Sweet CS: Controlled trial of losartan gives concomitantly with different doses of hydrochlorothiazide in hypertensive patients. *Blood Press* 1996;5:32-40.
36. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper ME. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ* 2000;321:1440-4.
37. Brenner BM, Cooper ME, 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;345:861-9.
38. Andersen S, Tarnow L, Rossing P, Hansen BV, Parving HH. Reno protective effects of angiotensin II receptor blockade in type 1 diabetic patients with diabetic nephropathy. *Kidney Int* 2000;57:601-6.
39. Lacourcière Y, Bélanger A, Godin C, Hallé J-P, Ross S, Wright N, Marion J. Long-term comparison of losartan and enalapril on kidney function in hypertensive type 2 diabetics with early nephropathy. *Kidney Int* 2000;58:762-9.
40. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000;342:905-912.
41. Wang JG, Staessen JA, Gong L, Liu L, for the Systolic Hypertension in China (Syst-China) Collaborative Group. Chinese trial on isolated systolic hypertension in the elderly. *Arch Intern Med* 2000;160:211-20.
42. Bakris GL, Williams M, Dworkin L *et al.* For the National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis* 2000;36:646-61.
43. Hansson L, Hedner T, Lund-Johansen P *et al.* Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular mortality in hypertension: the Nordic Diltiazem Study. *Lancet* 2000;356:359-64.
44. Giugliano D, Acampora R, Marfella R *et al.* Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension. A randomised, controlled trial. *Ann Intern Med* 1997;126:955-9.
45. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997;157:2413-46.
46. Lindholm LH, Hansson L, Ekbom T *et al.* Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J *Hypertens* 2000;18:167.
47. Lewis EJ, Hunsicker LG, Clarke WR *et al.* Reno protective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
48. Lindholm LH, Ibsen H, Dahlöf B *et al.* Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;359:1004-10.
49. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002;288:2981-97.50.