

Efficacy and Tolerability of Different Antihypertensive Drugs in Diabetic Patients with Mild to Moderate Hypertension in a Multi Speciality Hospital - A Prospective Comparative Study

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ABSTRACT

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Aim: To compare the efficacy and tolerability of different antihypertensive drugs in diabetic patients with hypertension. **Materials and methods:** A prospective, comparative study was conducted in 370 diabetes patients suffering from mild to moderate hypertension of either sex aged between 30-80 years. Patients with systolic blood pressure (SBP) above 130 mm Hg and patients with diastolic blood pressure (DBP) above 80 mm Hg were included in the study. Drugs used were ACE Inhibitor (ACE I), Beta blocker (BB), Calcium channel blocker (CCB) and Diuretic in monotherapy (n=134) and in 2 and 3 drugs combination (n=236). After 8 weeks of therapy patients were assessed for efficacy and tolerability. **Results:** Males were 51.3% and females 48.6%. There was a significant control ($P < 0.01$) in mean blood pressure in 90% of patients. Highest decrease in SBP was seen with ACE I+BB+Diuretic combination (39%) and in DBP with CCB+Diuretic combination (18.8%). A total of 74.5% of patients were prescribed ACE I in monotherapy and combination therapy groups. Adverse drug reactions (ADRs) reported were pedal edema, dry cough, headache, dizziness and muscle cramps. **Discussion and conclusion:** All the drug groups from monotherapy and combination therapy reduced BP effectively. Most effective groups were ACE I+BB+Diuretic and CCB+Diuretic combination. ACE I was effective and most frequently used drug. Two drug combination therapies were commonly prescribed – 50.2%.

Keywords: Hypertension, blood pressure, diabetes, monotherapy, combination therapy.

INTRODUCTION

Hypertension in diabetes is one of the most widespread, substantial and treatable cardiovascular risk factors of importance in clinical practice. As the number of diabetes patients increases on a global scale, so too does the number of patients with concomitant hypertension. Data from randomised trials have increasingly shown the benefits of tight blood pressure control in patients with type 2 diabetes.¹

Management of hypertension in diabetics demands special attention, more so in Indian scenario. Higher prevalence of hypertension amongst diabetics in India has been reported since 1985.² The presence of hypertension in diabetic patients substantially increases the risks of coronary heart disease, stroke, nephropathy and retinopathy. Indeed, when hypertension coexists with diabetes, the risk of

cardiovascular disease is increased by 75%, which further contributes to the overall morbidity and mortality of an already high-risk population.³

In general, only 25 percent of patients with hypertension have adequate control of their blood pressure.⁴ Blood pressure goals are lower, and thus more difficult to achieve, in patients who also have diabetes. Elevated blood pressure is known to contribute to diabetic microvascular and macrovascular complications. Fortunately, reductions in blood pressure can decrease the risk of these complications.⁵

Numerous national and international guidelines exist for the management of hypertension. Currently, the most influential guidelines in the United States addressing the appropriate treatment of hypertension in patients with diabetes are the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines (JNC-7),⁶ National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines,⁷ and American Diabetes Association (ADA) guidelines.⁸

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Rigorous blood pressure control to the targets recommended in treatment guidelines is paramount for reducing the progression of diabetic nephropathy to End Stage Renal Disease (ESRD). The JNC-7⁶ NKF KDOQI,⁷ and ADA⁸ guidelines all recommend a blood pressure goal of <130/80 mm Hg in patients with diabetes (versus <140/90 mm Hg for patients without diabetes) to optimally preserve renal function and reduce cardiovascular events.

Although a number of monotherapies and multidrug therapies are available for the treatment of hypertension, current guidelines provide evidence-based recommendations for the use of specific antihypertensive agents in patients with diabetes. The JNC-7,⁶ KDOQI,⁷ and ADA⁸ guidelines recommend the use of either ACE Inhibitors (ACEIs) or Angiotensin Receptor Blockers (ARBs) as initial therapy to achieve the blood pressure target in patients with type 2 diabetes mellitus. If one class is not tolerated, the other should be substituted if it is not contraindicated. Neither ACE inhibitors nor ARBs appear to produce any clinically significant changes in metabolic measurements, such as blood glucose and the lipid profile, which is an important consideration in the presence of diabetes.

Most patients with diabetes will require two or more antihypertensive therapies from different classes with complementary mechanisms of action to control their blood pressure.⁹ Thiazide diuretics, β -blockers, or calcium channel blockers (CCBs) can be added to ACE inhibitor or ARB treatment to achieve target blood pressure, either as an individual drug component or as part of a fixed-dose combination product.^{6,7,8}

The choice and doses of drugs used in combination therapy should be such that their synergistic effect on blood pressure is maximised, the tolerability of the drugs is maintained and side effects are minimized. The present study was designed to assess the drug use pattern of antihypertensive agents in diabetic patients with hypertension, to evaluate the tolerability and cost effectiveness related to hypertension and their effect on therapy.

MATERIALS AND METHODS

It was a prospective and comparative study carried out at Apollo K.H Hospital, Melvisharam, Tamilnadu, India. Diabetic patients of either sex aged between 30-80 years suffering from mild to moderate hypertension were selected from General Medicine and Pharmacy outpatients units. Patients with systolic blood pressure above 130 mmHg and diastolic blood pressure above 80 mmHg were included in the study. Pregnant and lactating women were excluded from the study. Patients declared their willingness to participate in the

study and written informed consent was obtained from them. Patients who fulfilled inclusion and exclusion criteria were enrolled in the study. Complete medical history, physical examination, concomitant diseases and medication taken, ECG (electrocardiogram) and baseline blood pressure, were recorded in the case record form. The following baseline investigations were done such as random blood sugar, blood urea, serum creatinine, serum electrolytes, serum cholesterol, serum bilirubin, serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT).

Depending on the severity of hypertension, patients were prescribed antihypertensive drugs either as monotherapy or combination therapy in (2 and 3 drug combination). Drugs included in the treatment were ACE Inhibitor 5mg once daily orally, Beta blocker 50mg once daily orally, Calcium channel blocker 10mg thrice daily orally and Diuretic 40mg twice daily orally. Drugs used in monotherapy included ACE Inhibitor and Beta blocker, while in combination therapy included ACE Inhibitor, Beta blocker, Calcium channel blocker and Diuretic. A+B, A+D, B+D, A+C, B+C, C+D, A+B+D, A+B+C and A+C+D combination were prescribed. After two months of therapy, patient's response to the ongoing antihypertensive treatment was checked by obtaining BP (though BP was checked every two weeks for the duration of the study), their baseline ECG and biochemical parameters were repeated. Patient's compliance to medication was recorded. They were interrogated for any adverse effects. A decrease in blood pressure (SBP <130 mmHg and DBP <80 mmHg) was the primary outcome measure. Secondary outcome measures were a) Safety variables including incidence, nature and intensity of adverse drug reactions (ADRs)-dry cough, pedal edema, dizziness, rash, flushing and diarrhoea. b) Changes in ECG and biochemical parameters.

Statistical Analysis: All the values were expressed as Mean $\pm$ SD. Parametric test was done using Student's Paired 't' test. P value <0.05 was considered as significant with 95% Confidence Interval.

RESULTS

A total of 370 patients participated in the present study. Out of which 190 (51.3%) were males and 180 (48.6%) were females. The demographic data of all the patients is shown in Table-1.

Table 1 Demographic data (n=370)

S. No	Age in years	No. of patients	Male	Female
1	30 - 40	0	06	04
2	41 - 50	38	24	14
3	51 - 60	96	38	58
4	61 - 70	148	78	70
5	71 - 80	78	44	34

Patients were divided in different groups on the basis of monotherapy and combination therapy. 36.21% patients belonged to monotherapy group and 63.78% patients belonged to combination therapy group.

Monotherapy group: n = 134 (36.21%)

ACE inhibitor – n = 76

Beta blocker – n = 58

Combination therapy group: n = 236 (63.78%)

1. Two drug combination therapy, n = 186 (50.27%)

ACE inhibitor + Beta blocker – n = 88

ACE inhibitor + Diuretic – n = 34

Beta blocker + Diuretic – n = 14

ACE inhibitor + Calcium channel blocker – n = 28

Beta blocker + Calcium channel blocker – n = 14

Calcium channel blocker + Diuretic – n = 08

2. Three drug combination therapy, n = 50 (13.51%)

ACE inhibitor + Beta blocker + Diuretic – n = 34

ACE inhibitor + Beta blocker + Calcium channel blocker – n = 10

ACE inhibitor + Calcium channel blocker + Diuretic – n = 06

Effect on systolic blood pressure: A highly significant decrease in mean SBP was observed with ACE I and BB monotherapy groups ($P < 0.001$). Similarly there was highly significant decrease ($P < 0.001$) observed with A+B, A+D, A+C, A+B+D, A+B+C and A+C+D combination therapy whereas there was significant reduction with B+D, B+C and C+D groups. (Table - 2)

Effect on diastolic blood pressure: A highly significant decrease in mean DBP was seen in monotherapy groups ($P < 0.001$). There was also highly significant reduction ($P < 0.001$) in A+B, A+D, B+C, C+D, A+B+D and A+B+C combination groups. Other combination groups showed a significant reduction with B+D, A+C and A+C+D combination groups. (Table - 3)

Table 2: Effect of drugs on systolic blood pressure (n=370)

Drugs	Systolic BP		Decrease in SBP	% decrease in SBP	95% CI		p value
	Baseline	After treatment			Baseline	After treatment	
Monotherapy							
A (n=76)	158.6 ± 30.86	129.7 ± 9.41	28.94 ± 4.03	28.5	150.9 ± 166.3	127.3 ± 132.0	<0.001
B (n=58)	162.3 ± 23.55	131.1 ± 9.00	31.17 ± 3.63	31.1	155.4 ± 169.1	128.5 ± 133.7	<0.001 2
Combination therapy							
A+B (n=88)	158.9 ± 26.32	131.1 ± 12.88	27.78 ± 6.90	27.7	145.8 ± 172.0	124.7 ± 137.5	<0.001
A+D (n=34)	146.6 ± 12.02	123.7 ± 5.53	22.92 ± 2.70	22.9	141.5 ± 151.7	121.3 ± 126.0	<0.001
B+D (n=14)	168.5 ± 30.55	132.0 ± 11.14	36.50 ± 11.50	36.5	143.0 ± 194.0	122.7 ± 141.3	0.006
A+C (n=28)	160.3 ± 27.59	131.1 ± 12.38	29.21 ± 3.42	29.2	154.0 ± 166.5	128.3 ± 133.8	<0.001
B+C (n=14)	158.6 ± 28.52	131.7 ± 10.27	26.86 ± 8.10	26.8	142.1 ± 175.0	125.8 ± 137.6	0.002
C+D (n=08)	155.0 ± 17.73	128.0 ± 9.04	27.00 ± 7.03	27.0	140.2 ± 169.8	120.4 ± 135.6	0.001
3 Combination therapy							
A+B+D (n=34)	175.0 ± 17.32	136.0 ± 4.61	39.00 ± 8.96	39.0	147.4 ± 202.6	128.7 ± 143.3	<0.001
A+B+C (n=10)	151.2 ± 17.78	127.0 ± 8.35	24.19 ± 3.47	24.1	144.8 ± 157.6	124.0 ± 130.0	<0.001
A+C+D (n=06)	140.8 ± 0.95	121.5 ± 0.57	19.25 ± 0.55	18.5	139.2 ± 142.3	120.6 ± 122.4	<0.001

A – ACE inhibitor, B – Beta blocker, C – Calcium channel blocker, D – Diuretic;
CI – confidence interval (lower & upper limits), SBP – systolic blood pressure; Values are expressed as mean ± SD

Table 3: Effect of drugs on diastolic blood pressure (n=370)

Drugs	Diastolic BP		Decrease in DBP	% decrease in DBP	95% CI		p value
	Baseline	After treatment			Baseline	After treatment	
1. Monotherapy							
A (n=76)	96.88 ± 16.22	80.94 ± 7.70	15.94 ± 2.24	15.9	92.82 ± 100.9	79.01 ± 82.86	<0.001
B (n=58)	97.92 ± 15.15	79.58 ± 8.98	18.33 ± 2.54	18.3	93.52 ± 102.3	76.98 ± 82.19	<0.001
2. Combination therapy							
A+B (n=88)	92.50 ± 6.07	77.50 ± 6.42	15.00 ± 1.80	15.0	89.93 ± 95.07	74.79 ± 80.21	<0.001
A+D (n=34)	99.90 ± 14.28	81.60 ± 8.43	18.29 ± 1.87	18.3	96.68 ± 103.1	79.70 ± 83.50	<0.001
B+D (n=14)	100.0 ± 13.09	83.75 ± 11.57	16.25 ± 6.17	16.2	89.05 ± 110.9	74.07 ± 93.43	0.019
A+C (n=28)	97.14 ± 14.37	80.00 ± 10.00	17.14 ± 4.68	17.1	88.84 ± 105.4	74.23 ± 85.77	0.001
B+C (n=14)	92.22 ± 2.55	75.00 ± 4.20	17.22 ± 1.15	15.5	90.95 ± 93.49	72.91 ± 77.09	<0.001
C+D (n=08)	96.00 ± 8.15	77.14 ± 7.26	18.86 ± 2.91	18.8	91.29 ± 100.7	72.95 ± 81.34	<0.001
3. Combination therapy							
A+B+D (n=34)	96.67 ± 5.16	78.33 ± 6.83	18.33 ± 3.49	18.3	91.25 ± 102.1	71.16 ± 85.50	<0.001
A+B+C (n=10)	95.00 ± 5.34	77.50 ± 5.97	17.50 ± 2.83	17.5	90.53 ± 99.47	72.50 ± 82.50	<0.001
A+C+D (n=06)	92.50 ± 2.88	77.50 ± 2.88	15.00 ± 2.04	15.0	87.91 ± 97.09	72.91 ± 82.09	0.003
A – ACE inhibitor, B – Beta blocker, C – Calcium channel blocker, D – Diuretic; CI – confidence interval (lower & upper limit), DBP – diastolic blood pressure; Values are expressed as mean ± SD							

A total of 90% of patients showed significant control in BP after 8 weeks of therapy. In both monotherapy and combination therapy ACEI was used most frequently in 74.5% followed by Beta blocker 58.9%, Diuretic 25.9% and Calcium channel blocker 17.8%. Few patients were on concomitant medication. Aspirin was prescribed to 60 patients, statins to 68 patients and aspirin + statin to 242 patients. As many as 110 (29.7%) of patients were without any co-existing diseases. 208 patients (56.2%) had Coronary artery disease (CAD), 52 patients (14.0%) were suffering from cerebrovascular accident (CVA).

No serious adverse drug reactions were reported. Some of the common ADRs reported were pedal edema, headache, dry cough, dizziness and muscle cramps/myalgia. However percentage of ADRs increased when given in combination therapy. Biochemical parameters were within normal limits. Patients' compliance was good.

DISCUSSION

In the present study most common classes of antihypertensive drugs such as Angiotensin Converting Enzyme Inhibitors (ACEIs), Calcium Channel Blockers (CCBs), Beta-blockers (BBs), and Diuretics were used to treat mild to moderate hypertension in diabetes patients. Differences between antihypertensive drugs were assessed principally by comparing their antihypertensive efficacy and tolerability. All the drug groups were shown to be effective in controlling BP.

We used the same classes of drugs in our study, which were given in JNC 7 classification of antihypertensive drugs. Our results were consistent with the previous studies where they used the same classes of drugs.^{10,11}

ACE inhibitors are considered preferred therapy in patients with hypertension and diabetes, according to guidelines from the ADA, the NKF, the World Health Organization, and the JNC VI.^{12,13,14,4} Findings from the Heart Outcomes Prevention Evaluation (HOPE) study also support the above recommendations.¹⁵ This trial showed a reduction in cardiovascular events in patients taking a maximum dosage of ACE inhibitors. Our study also shows that ACE inhibitors were the most frequently used drug in both monotherapy and combination therapy.

There have been several studies using combination therapy compared to monotherapy to assess cardiovascular outcomes in hypertensive patients, which have demonstrated a greater reduction of cardiovascular events with a combination of two agents than with each of the components. Recently, a meta-analysis of trials evaluating the use of antihypertensives in high-risk patients, including those with diabetes, showed that ACE inhibitor therapy resulted in a 20 to 30 percent decrease in the risk of stroke, coronary heart disease, and major cardiovascular events.¹⁶ A second meta-analysis compared ACE inhibitors with other antihypertensive agents in patients with diabetes.¹⁷ Three of the four studies evaluated showed ACE inhibitors to be of significantly greater benefit when

compared with other antihypertensives in the reduction of acute myocardial infarction, cardiovascular events, and all-cause mortality. In our study we noted that majority of patients were on 2 drug combination therapy, mostly with ACE inhibitor, Beta blocker or diuretic combination, hence supporting the above studies.

Studies conducted previously showed that BB reduced mean SBP by 18.2 ± 11.3 mmHg¹⁸ and ACE I by 10.0 ± 2.0 mmHg,¹⁹ whereas in our study BB and ACE I monotherapy reduced mean SBP by 31.1 ± 3.6 mmHg and 28.9 ± 4.0 mmHg respectively, which showed more effective reduction than previous studies. Edward et al found reduction in mean SBP by 18.0 mmHg with BB+CCB combination²⁰. Our study showed 26.8 mmHg reductions, which was more effective reduction than the above study. There was significant reduction of 22.9 ± 2.7 mmHg in mean SBP with ACE I and Diuretic combinations in diabetic patients with moderate hypertension. Similarly in one study there was effective reduction of mean SBP in moderate HTN with ACE I and a diuretic combination.²⁰

In our study, combination of ACE I+BB reduced mean SBP by 27.7 ± 6.9 mmHg whereas ACE I alone in monotherapy showed 28.9 ± 4.0 mmHg reduction. We found that monotherapy with ACE inhibitor was more effective than combination of ACE inhibitor with BB. Wing et al found that the combination of ACE I+BB to be largely ineffective when compared to ACE I alone²¹ hence supporting our study. Several studies reported that the combination of ACE I with dihydropyridine CCB was especially effective.^{22, 23} Our study also showed effective reduction in mean SBP by 29.2 ± 3.4 mmHg with ACEI+CCB combination. Reduction in mean SBP with ACE I+BB+CCB was 24.1 ± 3.4 mmHg, while ACEI+BB+Diuretic combination showed 39.0 ± 8.9 mmHg reduction. Previous studies were also reported that the combination of an ACE I plus BB plus Diuretic was more effective than an ACE I plus BB plus CCB^{24,25} hence supporting our study.

In the present study we found significant reduction in mean DBP with both monotherapy as well as combination therapy. Previous studies reported 11.5 ± 8.3 mmHg and 8.0 ± 1.0 mmHg reduction of mean DBP with BB and ACEI monotherapy respectively,^{18, 19} whereas our study showed 18.3 ± 2.5 mmHg and 15.9 ± 2.5 mmHg reduction in mean DBP with BB and ACEI monotherapy, which showed more effective reduction than previous studies. In a previous study there was 13.0 mmHg fall in mean DBP with BB+CCB combination,²⁰ we observed more effective reduction of 17.2 ± 1.1 mmHg with the same combination therapy. Effective

reduction in mean DBP was seen with ACEI+CCB, ACEI+Diuretic and BB+Diuretic combination therapy which were 17.1 ± 4.6 mmHg, 18.2 ± 1.8 mmHg and 16.2 ± 6.1 mmHg respectively. Previous studies also proved effective reduction with the above combination therapy.^{19,21} Combination of ACE I+BB+Diuretic showed 18.3 ± 3.4 mmHg reduction in means DBP whereas ACE I+BB+ CCB showed reduction of 17.5 ± 2.8 mmHg. Our results support the previous studies^{24,25} which reported that ACE I+BB+Diuretic is more effective than ACE I+BB+CCB combination and we also found the same results with mean SBP with the above combination therapy.

We observed that combination therapy was used for both mild and moderate HTN. Among all the groups ACE I+BB+Diuretic combination was highly effective in reducing SBP and CCB+Diuretic was highly effective in reducing mean DBP.

It was noted that diabetic patients with HTN were mostly given ACE I. Patients with CAD and CVA were on ACE I+BB. We had observed that there was frequent use of ACE I in various comorbid conditions associated with HTN. According to JNC 7 classification, compelling indication for use of ACEIs are CVA, CAD, DM, heart failure and chronic kidney disease. Hence ACEIs are a valuable addition to the pharmacotherapy of HTN.⁶ These studies recommended better adherence to JNC 7 guidelines.

In addition to antihypertensive drugs, patients were advised to take adjuvant therapy like aspirin and statins. Several studies demonstrated that use of aspirin leads to 16% reduction in all cardiovascular events and 20% reduction in myocardial infarction in hypertensive patients.^{26, 27} HTN and hypercholesterolemia often co-exist as risk factor and one study (ASCOTLLA) observed the benefits of lipid lowering therapy in hypertensive patients.²⁸

Patients on ACE I monotherapy (20%) complained of dizziness and this was increased with combination ACE I+CCB+Diuretic. Pedal oedema was reported by 22% of patients, who were on CCB treatment. No serious ADRs were observed in our study. Most frequently encountered side effect with ACE was dry cough (10%). Constipation, pedal edema and headache were reported in patients who were on CCB. Patients with BB, CCB and Diuretic combination therapy complained of myalgia and dizziness, which are all predictable ADRs.

Life style modifications also termed as non-pharmacological therapy can decrease and help in controlling BP. These changes are useful when implemented in conjunction with drug therapy. They can enhance the efficacy of

antihypertensive agents and decrease cardiovascular risks and may even reduce the number of required drugs and their dosage. Major life style modifications include weight reduction in those individuals who are overweight or obese²⁹ and adoption of Dietary approaches to Stop Hypertension (DASH) eating plan which is rich in potassium, calcium and dietary sodium reduction and physical activity^{30, 31, 32} which have shown to achieve better results in lowering BP.

CONCLUSION

There is a strong epidemiological connection between hypertension in diabetes and adverse outcomes of diabetes. Clinical trials demonstrate the efficacy of drug therapy in reducing these outcomes and in setting an aggressive blood pressure-lowering target of <130/80 mmHg. It is very clear that many people will require three or more drugs to achieve the recommended target. Achievement of the target blood pressure goal with a regimen that does not produce burdensome side effects and is at reasonable cost to the patient is probably more important than the specific drug strategy.

Because many studies demonstrate the benefits of ACE inhibitors on multiple adverse outcomes in patients with diabetes, including both macrovascular and microvascular complications, in patients with either mild or more severe hypertension and in both type 1 and type 2 diabetes, the established practice of choosing an ACE inhibitor as the first-line agent in most patients with diabetes is reasonable.

We could conclude from our study that all groups in monotherapy and combination therapy were equally effective in reducing BP. Combination therapy was used in large proportion of patients to treat hypertension in diabetes, in which two drug combinations were used more. Monotherapy with ACE I was more effective than ACE I+ BB combination.

REFERENCES

1. Zanchetti A, Ruijlope L M. Antihypertensive treatment in patients with type-2 diabetes mellitus: what guidance from recent controlled randomized trials? *J Hypertens* 2002; 20: 2099-2110.
2. Patel JC. Diabetes and its complications. *J Diab Assn Ind* 1985; 25:16-25.
3. Sowers J R, Epstein M, Frohlich E D. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* 2001; 37(4):1053-1059.
4. 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.
5. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ* 1998; 317:713-20.
6. Chobanian AV, Bakris GL, Black HR et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC-7 report. *JAMA* 2003; 289:2560-72.
7. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43:S1-290.
8. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2005; 28:990.
9. Bakris GL. The importance of blood pressure control in the patient with diabetes. *Am J Med* 2004; 116:30S-8S.
10. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood pressure lowering drugs: results of prospectively designed overviews of randomized trials. Blood pressure lowering treatment trialists' collaboration. *Lancet* 2000; 356:1955-1964.
11. Psaty BM, Smith NL, Siscovick DS et al. Health outcomes associated with antihypertensive therapies used as first line agents: A systematic review and meta analysis. *JAMA* 1997; 277:739-745.
12. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002; 25:213-29.
13. 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.
14. World Health Organization-International Society of Hypertension Blood Pressure Lowering Treatment Trialists' Collaboration. Protocol for prospective collaborative overviews of major randomized trials of blood-pressure-lowering treatments. *J Hypertens* 1998; 16:127-37.
15. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355:253-9.
16. 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.

17. Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Furberg CD. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. *Diabetes Care* 2000; 23:888-92.
18. Coats AJ, Bird AJ, Conway AJ. Safety of nifedipine in patients with hypertension. *J Hum Hypertens* 1989; 3(1):65-66.
19. Morgan T, Anderson A, Hopper J. Enalapril and nifedipine in essential hypertension; synergism of the hypotensive effects in combination. *Clin Exp Hypertension* 1988; 10(5):779-789.
20. Edwards KG, Tweed JA, Saul PA et al. A comparative study of atenolol/nifedipine and atenolol/diuretic in hypertension. *Pharmatherapeutica* 1986; 4:637-641.
21. Wing LMH, Chalmers JP, West MJ et al. Enalapril and atenolol in essential hypertension: attenuation of hypotensive effect in combination. *Clin Exp Hypertens* 1988; 10:119-133.
22. Guazzi MD, DeCesace N, Galli C et al. Calcium channel blockade with nifedipine and angiotensin converting enzyme inhibition with captopril in the therapy of patients with severe primary hypertension. *Circulation* 1984; 80:279-284.
23. Bevan ES, Pringle SD, Waller PC et al. Comparison of captopril, hydralazine and nifedipine as third drug in hypertensive patients. *J Hum Hypertens* 1993; 7:83-88.
24. McAreavey d, Ramsay LE, Latham L et al. Third drug trial: comparative study of antihypertensive agents added to treatment when blood pressure remains uncontrolled by a beta blocker plus thiazide diuretic. *BMJ* 1984; 288:106-111.
25. Jon O N. Do ACE Inhibitors decrease mortality in patients with hypertension? *American Family Physician* 2004; 70(1):153-154.
26. Thrombosis Prevention Trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998; 351(9098):233-241.
27. 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) randomized trial. *Lancet* 1998; 351(9118):1755-1762.
28. Oscende JI, Ruiz-Ortega M, Blanco-Colio LM et al. Statins to prevent cardiovascular events in hypertensive patients. The ASCOT-LLA study. *Nephrol Dial Transplant* 2004; 19(3):528-531.
29. He J, Whelton PK, Appel LJ et al. Long term effects of weight loss and dietary sodium reduction on incidence of hypertension. *Hypertension* 2000; 35:544-549.
30. Sacks FM, Svetkey LP, Vollmer WM. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-sodium collaborative research group. *N Engl J Med* 2001; 344(1):3-10.
31. Vollmer WM, Sacks FM, Ard J. Effects of dietary patterns and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001; 135:1019- 1028.
32. Kelley GA, Kelley KS. Progressive resistance exercise and resting blood pressure. *Hypertension* 2000; 35:838-843.