Journal of Basic and Clinical Pharmacy

www.jbclinpharm.com

A REVIEW OF ANTI-HYPERTENSION THERAPIES IN DIABETIC PATIENTS

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ABSTRACT: The objective of this study was to review published articles on the issues surrounding tight blood pressure control in hypertensive diabetics.

Relevant medical subject headings (MeSH) terms and keywords to review scientific literatures were developed. These MeSH terms were used to generate MEDLINE searches that focused on English-language, peer-reviewed scientific literature.

In reviewing the exceptionally large body of research literature in anti-hypertension therapies in diabetic patients , the review focused on outcomes of importance to patients and effects of sufficient magnitude to warrant changes in medical practice ("patient oriented evidence that matters" [POEMs]).

Patient-oriented outcomes include not only mortality but also other outcomes that affect patients' lives and well-being. Studies of physiological end points (disease-oriented evidence [DOEs]) were used to address questions where POEMs were not available.

Treatment of hypertension in diabetic patients provides dramatic beneficial outcomes. Target diastolic BP of < 80 mmHg appears optimal; and systolic targets of 130 mmHg or less are also reasonable. Studies that compare drug classes do not suggest obviously superior agents. However, it is reasonable to conclude that ACEIs, thiazide diuretics and angiotension II receptor blockers may be the preferred first-line agents for treatment of hypertension in diabetes. ACEIs, ARBs and low dose thiazide diuretics may be the first line treatments although other agents are usually necessary and goals may not be achieved even with three or four agents. Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in hypertensive patients with diabetes.

KEYWORDS: ACEIs, Diabetic patients, hypertension, hypertensive drugs, Review.

received on 29-04-2010
modefied on 18-05-2010
accepted on 21-05-2010
available online 15-08-2010
www.jbclinpharm.com

INTRODUCTION

Hypertension is an extremely common co-morbidity of diabetes affecting 20-60% of people with diabetes and it is also a major risk factor for cardiovascular events as well as for diabetic microvascular complications, such as retinopathy, nephropathy and possibly neuropathy [1,2]. These diabetic microvascular complications arise due to the fact that the tissues of the eyes, Kidneys and nerves do not require insulin for glucose uptake, as muscles and adipose tissues do, and therefore are exposed to an excess amount of glucose. Thus the occurrence of hypertension in association with diabetes mellitus constitutes one of the most rapidly increasing disorders in the world. Because the benefits of tight blood pressure (BP) control in patients with diabetes exceed the benefits of tight glycemic control, and extend to the prevention of both microvascular and macrovascular complications (Table 1). Some results of adequate evidence-based studies support an aggressive approach to the diagnosis and treatment of hypertension in reducing the incidence of such diabetic complications [3].

Among hypertensive diabetics, macrovascular complications are more common; up to 80% of patients with type 2 diabetes will develop or die of macrovascular disease [4], and the costs associated with

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Table 1: Microvascular and macrovascular complications of hypertension in patients with diabetes

Microvascular complications	Macrovascular complications
Renal disease: hypertension contributes to the risk of renal disease in patients with diabetes.	Cardiac disease: hypertension in patients with diabetes increases the risk of coronary artery disease, congestive heart failure, and cardiomyopathy.
Autonomic neuropathy.	
Sexual dysfunction: hypertension and antihypertensive therapies may independently contribute to autonomic associated sexual dysfunction in diabetes.	Cerebrovascular disease: hypertension increases the incidence of stroke in patient with diabetes.
Eye disease: hypertension increases the risk of eye diseases in patients with diabetes, including glaucoma and diabetic retinopathy with potential blindness.	Peripheral vascular disease: hypertension increases the risk of peripheral vascular disease and subsequent foot ulcers and amputation in patients with diabetes.33(01)

macrovascular disease are greater than those associated with microvascular diseases [5].

Hypertension in Diabetic Populations

Epidemiological studies and therapeutic trials have often used different criteria to define hypertension in diabetic patients. Studies in the general population indicate an increased risk of cardiovascular disease with an increase in level of blood pressure. Thus an increase in diastolic or systolic blood pressure of 5mmHg is associated with a concomitant increase in cardiovascular disease of 20-30% [6]. Studies in diabetic populations have shown a markedly higher frequency of the progression of diabetic retinopathy when diastolic blood pressure is in the excess of 70mmHg [7].

Most epidemiological studies have used a categorical definition of hypertension, using levels of 160mmHg for systolic and 90mmHg for diastolic blood pressure. Based on the evidence from clinical trials showing clinically significant benefits of treating diabetic individuals to lower levels of blood pressure, these values are considered too high to serve as threshold for the definition of hypertension in diabetic patients.

However, the standard definition of hypertension by the JNC-VII [1] is a blood pressure (BP) ≥ 140/90mmHg for the general population and they recommended a lower target (130/80mmHg) for diabetic patients. Because of the high cardiovascular risk associated with BP ≥ 130/80mmHg in patients with diabetes, 130/80mmHg is considered to be the cut point for defining diabetic hypertension, rather than 140/90mmHg, as in the general population.

Prevalence of Hypertension in Diabetic Populations

The prevalence of hypertension in the diabetic population is 1.5-3 times higher than that of non diabetic age-matched groups [8]. Hypertension ultimately affects approximately 30% of individuals with type 1 DM and approximately 20-60% of patients with type 2 DM will develop hypertension depending on age, ethnicity and obesity [1].

Type 2 diabetes constitutes over 90% of diabetes in the United States and is associated with a 70% to 80% chance of premature death from CVD and stroke [9-13]. The concordance of hypertension and diabetes is increased in the population; hypertension is disproportionately higher in diabetics [14], while persons with elevated BP are 2.5 times more likely to develop diabetes within 5 years [15,16]. The common absence of normal nocturnal "dipping" of BP in diabetics is linked to other CVD surrogates such as left ventricular hypertrophy (LVH) and microalbuminuria [14].

The coexistence of hypertension in diabetes is particularly pernicious because of the strong linkage of the 2 conditions with all CVD [11,12], stroke [11,12,17-19,20-22] progression of renal disease [21,23-25], and diabetic retinopathy [26]. The United Kingdom Prospective Diabetes Study (UKPDS) [20] demonstrated that each 10 mm Hg decrease in SBP was associated with average reductions in rates

of diabetes-related mortality of 15%; myocardial infarction, 11%; and the microvascular complications of retinopathy or nephropathy, 13%.

Screening and Initial Evaluation:

A complete medical history with special emphasis on cardiovascular risk factors and the presence of diabetic and other cardiovascular complications should be assessed initially. Blood pressure should be measured at every routine diabetes visit and should ideally be measured in the supine and standing position in order to detect the presence of autonomic neuropathy because the presence of postural hypotension should be taken into consideration when anti-hypertensive drugs are to be chosen. The diagnosis of hypertension in patients with diabetes should be reserved for those individuals whose blood pressure levels exceed 130/80mmHg on at least two separate occasions separated by at least one week. Initial laboratory examination should include Fasting blood sugar, oral glucose tolerance test, serum creatinine, electrolytes, HbAlc, lipid profile, and urinary albumine excretion. The aim was to review published articles on the issues surrounding tight blood pressure control in hypertensive diabetics.

DATA SYNTHESIS

Relevant medical subject headings (MeSH) terms "diabetic patients" and keywords "antihypertensive drugs" to review scientific literatures were developed. These MeSH terms and key words were used to generate MEDLINE searches that focused on English-language, peer-reviewed scientific literature from January 2000 through December 2008.

In reviewing the exceptionally large body of research literature in anti-hypertension therapies in diabetic patients , the review focused on outcomes of importance to patients and effects of sufficient magnitude to warrant changes in medical practice ("patient oriented evidence that matters" [POEMs]) [27,28].

Patient-oriented outcomes include not only mortality but also other outcomes that affect patients' lives and well-being. Studies of physiological end points (disease-oriented evidence [DOEs]) were used to address questions where POEMs were not available.

DISCUSSION

Non Pharmacological Management: Behavioral Treatments

Diabetic patients with a BP of 130-139/80-89mmHg should be given lifestyle therapy alone for a maximum of three months and then, if targets are not achieved, should also be treated pharmacologically. Sodium restriction has not been tested in diabetic population in controlled clinical trials. However, in essential hypertension there has been reduction in systolic blood pressure of approximately 5mmHg and diastolic blood pressure of 2-3mmHg with moderate sodium restriction. Even when pharmacologic agents are used, there is often a better response when there is concomitant salt restriction due to the volume component of hypertension that is almost always present [29]. Since weight reduction can reduce blood pressure and improve blood glucose, control lipid levels and improve insulin sensitivity, it should be considered an effective measure in the initial management of mild-to-moderate hypertension.

The loss of 1Kg body weight has resulted in decreases in mean arterial blood pressure of approximately 1mmHg. Moderately intense physical activity, such as 30-45 min of brisk walking most days of the week, has been shown to lower blood pressure and is recommended in the JNC-VII [1]. The American diabetes Association (ADA) [2] has recommended that diabetic patients who are 35 years of age or older and are planning to begin a vigorous exercise program should have exercise stress testing or other appropriate non-invasive testing. Smoking cessation and moderation of alcohol intake are also recommended by JNC-VII to reduce blood pressure and are clearly appropriate for all patients with diabetes. These non pharmacological strategies may also positively affect glycemia and lipid control [1].

DRUG THERAPY OF HYPERTENSION IN DIABETES

ACE- Inhibitors

All patients with diabetes and hypertension should be treated with an antihypertensive regimen that includes either an ACE inhibitor or an ARB [30]. Pharmacologically, both these agents should provide nephroprotection owing to vasodilation in the efferent arteriole of the kidney. Moreover, ACE inhibitors have overwhelming data demonstrating

cardiovascular risk reduction in patients with established forms of heart disease.

These drugs are useful in the management of hypertension in diabetic patients who have had a myocardial infarction or congestive heart facture. They are also employed in patients with or without nephropathy. ACE-inhibitors have been extensively studied in the treatment of diabetic nephropathy and are effective in preventing progression of retinopathy. ACE-inhibitors have beneficial effects in diabetic patients and that such benefits are independent of their antihypertensive properties. Furthermore, these agents are considered preferred therapy in hypertensive diabetics [3, 31, 32].

A meta-analysis of trials evaluating the use of antihypertensive in high risk patients including those with diabetes in which the ACE inhibitor therapy resulted in a 20 to 30 percent decrease in the risk of stroke, coronary heart disease and major cardiovascular events [33]. However, the study conducted by the UKPDS (United Kingdom Prospective Diabetes Study) in which the ACEI, Captopril was compared with the B-blocker, Atenolol showed the two agents to be similar in terms of reduction in macrovascular and microvascular complications [34].

Postulated mechanisms of action of ACEIs include effects on the endothelium as a result of decreased vascular smooth muscle growth, decrease release of endothelin, increased fibrinolysis, and release of the vasodilatng substances: nitric oxide and prostacyclin mediated by bradykinin. The side effects of ACEIs include cough, angioedema and acute decreases in renal function.

Diuretics

Diuretics, preferably a thiazide, are fist-line agents for most patients with hypertension [1]. The best available evidence justifying this recommendation is from ALLHAT [18]. Moreover, when combination therapy is needed in hypertension to control BP, a diuretic is recommended as one of the agents used [1].

Thiazide diuretics have been shown to be of immense benefit to patients with diabetes and systolic hypertension. The systolic Hypertension in the Elderly Program (SHEP) [35,36] trial was established to assess the effect of low dose diuretic-based antihypertensive therapy on the rates of major cardiovascular events in older patients with isolated systolic hypertension and diabetes. At the end of the study, it was discovered that low-dose Chlorthalidone therapy was effective in preventing major cardiovascular events in older non-insulin treated patients with diabetes and isolated systolic hypertension. Thiazide diuretics, when given in very low dosages, (e.g hydrochlorothiazide 12.5mg per day) are generally well tolerated and not associated with adverse metabolic effects.

This class of diuretics is not as effective in patients with renal insufficiency; in such; patient, loop agents, say frusemide are preferred.

Diuretics are said to be superior to α-blockers, CCBs, and ACEIs in preventing one or more forms of CVDs, including stroke and heart failure [37, 38] and its low cost which is well appreciated in such an economy.

The exact hypotensive mechanism of action of diuretics is not known but has been well hypothesized. The drop in BP seen when diuretics are first started is caused by an initial diuresis. Diuresis causes reductions in plasma and stroke volume, which decreases cardiac output and BP. This initial drop in cardiac output causes a compensatory increase in peripheral vascular resistance.With chronic diuretic therapy, extracellular fluid and plasma volume return to near pretreatment values. However, peripheral vascular resistance decreases to values that are lower than the pretreatment baseline. This reduction in peripheral vascular resistance is responsible for chronic antihypertensive effects. Thiazide diuretics have additional actions that may further explain their antihypertensive effects. Thiazides mobilize sodium and water from arteriolar walls. This effect would lessen the amount of physical encroachment on the lumen of the vessel created by excessive accumulation of intracellular fluid. As the diameter of the lumen relaxes and increases, there is less resistance to the flow of blood, and peripheral vascular resistance drops further. High dietary sodium intake can blunt this effect, and a low salt intake can enhance this effect. Thiazides also are postulated to cause direct relaxation of vascular smooth muscle. This theory is based on the known mechanism of action of diazoxide, which is a direct vasodilator that is structurally related to thiazide diuretics.

Angiotensin Receptor Blockers (ARBs)

Studies have shown that losartan, irbesartan and valsartan therapies produced a renoprotective effects

and microalbuminuria reduction independent of their blood pressure lowering effects in patients with type 2 diabetes and nephropathy. Valsartan lowered urine albumin excretion to greater degree than amlodipine in type 2 diabetic patients who have concomitant microalbuminuria [39-41].

Calcium Channel Blockers (CCBs)

There are many controversies surrounding the use of the CCBs particularly the dihydropyridines in treating hypertension in patients with diabetes. Some studies have evaluated cardiovascular outcomes in patients with hypertension and diabetes who were treated with dihydropyridine CCBs. Both the Appropriate Blood pressure Control in Diabetes (ABCD) trial [42] and the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) [43] demonstrated no significant reduction in cardiovascular events with a dihydropyridine CCB compared with an ACE inhibitor.

On the other hand, the Hypertension Optimal Treatment (HOT) trial [17], and the isolated systolic Hypertension in china study [44], concluded that the use of dihydropyridine CCBs, as monotherapy or in combination with another agent, was associated with a reduction in cardiovascular risk.

In these studies, the decreased cardiovascular risk appeared to result from achievement of target blood pressure, rather than from intrinsic characteristics of the agent(s) used. In all the trials, many patients required the addition of an ACEI or other antihypertensive to the dihydropyridine CCB to achieve target blood pressure goals. The comnination of an ACEI and a dihydropyridine CCB has been shown to reduce proteinuria [45].

The trials reported that non dihydropyridine CCBs (eg varapamil and Diltiazem) demonstrated reductions in cardiovascular risk when used as monotherapy. Combining a non dihydropyridine CCB with an ACEI in hypertensive diabetics is associated with greater reductions in proteinuria than if either agent is used alone.

Beta Blockers (β-Blockers)

In randomized studies involving hypertensive diabetics, in which proteinuria was examined, the $^{\beta}$1-selective blocker atenolol produced similar reductions in proteinuria compared with an ACE inhibitor. In the UKPDS-HDS (hypertension in Diabetes study), the $^{\beta}$1-blocker atenolol and the ACEI captopril were equally effective in decreasing the risk of diabetes-related end points and microvascular events in a large group of subjects with type 2 DM but the mean weight gain in the atenolol group was greater [32,33]. Although the UKPDS study did not show an increased incidence of hypoglycemic episodes in the group treated with $^{\beta}$1-blockers, it is probably prudent to avoid the use of $^{\beta}$-blockers in insulin-using patients who have a history of severe hypoglycemia. In other patients with diabetes, especially patients with a recent myocardial infarction where $^{\beta}$-blockers have demonstrated efficacy with relative reductions in mortality of approximately 25%, the benefits of $^{\beta}$-blockers would appear to outweigh the potential risks [1].

Alpha Blockers (α-Blockers)

These drugs are no agents for first time treatment of hypertensive diabetics but may be combined with other agents to treat poorly controlled BP. They are also effective in treating patients with benign prostatic hypertrophy [46].

Combination of Antihypertensive Agents

Diuretic agents in combination with adrenergic blockers have been used in several nephropathy studies and in the UKPDS –HDS [34] and SHEP [35] study.

In general, combination therapy may help to improve compliance as one drug may antagonize the adverse effects of another. The superiority of one combination regime over another has not been documented.

There are supports from several randomized clinical trials for reducing systolic BP to ≤ 140mmHg and for reducing diastolic BP to ≤ 80mmHg. Epidemiological evidence demonstrates that BP ≥ 115/75mmHg is associated with increased cardiovascular event rates and mortality in diabetic patients. Therefore, a target blood pressure goal of < 130/80 mmHg is reasonable if it can be safely achieved. Although there is no threshold value for BP, whether even more aggressive treatment would reduce the risk further is an unanswered question. Achieving lower levels, however, would increase the cost of care as well as drug side effects and is difficult in practice. The ideal strategy for treating hypertension in persons with diabetes is still obscure. Initial therapy for those with BP ≥ 140/90mmHg should be with a drug

class shown to reduce CVD events in patients with diabetes which include ACEIs, ARBs, low does thiazide diuretics, β-blockers, and calcium channel blockers. Though there is no conclusive evidence favoring one class of drugs over others, it is now an established practice to begin hypertensive patients with diabetes but without microalbuminuria on an ACEI. When microalbuminuria or more advanced stages of nephropathy is present, both ACEIs (type I DM and type 2 DM patients) and ARBs (type 2 DM patients) are considered first line therapy for preventing the progression of nephropathy. If the target BP goal of < 130/80mmHg is not obtained with the initial doses of first line drugs, increases in doses are recommended, or the addition of a second drug from a different group should be considered. Regardless of the initial treatment, it must been emphasized that most patients will require more than two drugs to achieve the recommended target and many will require three or more. The achievement of the target BP may be more important than the particular drug regimen used. Thiazide diuretics (low dose) have been shown to improve cardiovascular outcomes and may address the volume or salt-sensitive components of hypertension, complimenting the mechanism of action of other drugs, so these are appropriate choices for a second or third drug and can also be used as an initial agent in patients who are not at risk of any cardiovascular events (eg. dyslipidemia) or proteinuria. Non-dihydropyridine calcium channel blockers susch as verapamil or diltiazem can be used when ACEIs, ARBs, or β-blockers are not tolerated or are contraindicated or when a second or third drug is required. Actually, classes of drugs for which there are no long term data on efficacy in improving outcomes can be used when there is intolerance to other classes, when there is specific indications for their use apart from treatment of hypertension (eg: α-blockers for patients with BPH and diltiazen for rate control in atrial fibrillation), or when additional drug are required to achieve the target blood pressure. Treatment decisions should however, be individualized based on the clinical characteristics of the patients, including comorbidities as well as tolerability, cost and in elderly hypertensive patients, BP should be lowered gradually to avoid complications [1].

CONCLUSION

Treatment of hypertension in diabetic patients provides dramatic beneficial outcomes. Target diastolic BP of < 80 mmHg appears optimal; and systolic targets of 130 mmHg or less are also reasonable. Studies that compare drug classes do not suggest obviously superior agents. However, it is reasonable to conclude that ACEIs, thiazide diuretics and angiotension II receptor blockers may be the preferred first-line agents for treatment of hypertension in diabetes. ACEIs, ARBs and low dose thiazide diuretics may be the first line treatments although other agents are usually necessary and goals may not be achieved even with three or four agents. Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in hypertensive patients with diabetes.

ACKNOWLEDGEMENT

I wish to acknowledge the efforts of my wife Mrs. Adibe O. C. and entire members of department of clinical pharmacy and pharmacy management, university of Nigeria, Nsukka.

REFERENCES

1. Chobanian AV, Bakris GL, Black HR, et al. JNC-7 Complete report: Prevention, Detection, Evaluation, And Treatment of High Blood Pressure. Hypertension. 2003; 42: 1206 –1252.
2. American Diabetes Association. Treatment of hypertension in adults with diabetes. Diabetes Care. 2003; 26: S80–S82.
3. Sherri LK. Victoria SD and David WB. Controlling hypertension in patients with diabetes. American family physician. 2002; 1209-1212.
4. Harris MI. Epidemiology of diabetes mellitus among the elderly in the United States. Clin Geriatr Med. 1990; 6: 703-19.
5. Economic consequences of diabetes mellitus in the U.S. American Diabetes Association. Diabetes care. 1998; 21: 296-309. From http://us.yhs.search.yahoo.com/avg/search?fr=yhs-avg&type=yahoo_avg_hs2-tb-web_us&p=Economic%20consequences%20of%20diabetes%20mellitus%20in%20the%20U.S.%20American%20Diabetes%20Association.%20%20Diabetes%20care.%201998.
6. Mac Mahon S, Peto R, Custler J. Collins R. et al. Blood pressure, stroke, and coronary heart disease. Part I. prolonged difference in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet. 1990; 335: 765-774.
7. Janka HU, Wavram JH, Rand LI, et al. Risk factors for progression of background retinopathy in long-standing IDDM. Diabetes. 1989; 38: 460-460.
8. Svetkey LP, Vollmer WM, Appel LJ, et al. 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: 3–10.
9. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic sub-

jects with and without prior myocardial infarction. N Engl J Med. 1998; 339: 229–234.
10. Assman G, Cullen P and Schulte H. The Munster Heart Study (PROCAM): results of follow-up at 8 years. Eur Heart J. 1998; 19: A2–A11.
11. Fagan TC and Sowers J. Type 2 diabetes mellitus: greater cardiovascular risks and greater benefits of therapy. Arch Intern Med. 1999; 159: 1033–1034.
12. Davis TM, Millns H, Stratton IM, et al. Risk factors for stroke in type 2 diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS) 29. Arch Intern Med. 1999; 159: 1097–1103.
13. Grundy SM, Benjamin IJ, Burke GL et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 1999; 100: 1134–1146.
14. Sowers JR and Haffner S. Treatment of cardiovascular and renal risk factors in the diabetic hypertensive. Hypertension. 2002; 40: 781–788.
15. Gress TW, Nieto FJ, Shahar E et al. 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.
16. Sowers JR and Bakris GL. Antihypertensive therapy and the risk of type 2 diabetes mellitus. N Engl J Med. 2000; 342: 969–970.
17. 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. HOT Study Group. Lancet. 1998; 351: 1755–1762.
18. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 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: 2981–2997.
19. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000; 342: 145–153.
20. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000; 321: 412–419.
21. UKPDS 38. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. BMJ. 1998; 317: 703–713.
22. Goldstein LB, Adams R, Becker K, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Circulation. 2001; 103: 163–182.
23. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000; 36: 646–661.
24. Maki DD, Ma JZ, Louis TA, et al. Long-term effects of antihypertensive agents on proteinuria and renal function. Arch Intern Med. 1995; 155: 1073–1080.
25. Nelson RG, Bennett PH, Beck GJ, et al. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. Diabetic Renal Disease Study Group. N Engl J Med. 1996; 335: 1636–1642.
26. Kohner EM, Aldington SJ, Stratton IM, et al. United Kingdom Prospective Diabetes Study, 30: diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. Arch Ophthalmol. 1998; 116: 297–303.
27. Shaughnessy AF, Slawson DC and Bennett JH. Becoming an information master: a guidebook to the medical information jungle. J Fam Pract. 1994; 39:489–499.
28. Slawson DC and Shaughnessy AF. Obtaining useful information from expert based sources. BMJ. 1997; 314: 947–949.
29. Arauz-Pacheco C. Parrott MA andn Raskin P. The treatment of Hypertension in Adult Patients with Diabetes. Diabetes care. 2002; 25: 134-145.
30. Arauz-Pacheco C, Parrott MA and Raskin P. Hypertension management in adults with diabetes. Diabetes Care .2004; 27(suppl 1): S65–67.
31. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. Am J kid Dis. 2000; 36: 646-661.
32. JNC 6. National High Blood Pressure Education Program. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med. 1997; 157: 2413–2446.
33. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet. 2000; 356: 1955–1964.
34. UK prospective Diabetes study Group. Efficacy of atenolol and captopril in reducing risk of macrovasculaar and microvasuclar complication in type 2 diabetes: UKPDS 39. BMJ. 1998; 317:713-20.
35. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991; 265:3255–3264.
36. Kostis JB, Davis BR, Cutler J, et al. Prevention of heart failure by antihypertensive drug treatment in older persons with isolated systolic hypertension. SHEP Cooperative Research Group. JAMA. 1997; 278: 212–216.
37. Fineberg SE. The treatment of hypertension and dyslipidemia in diabetes mellitus. Prim care. 1999; 26: 951-64.
38. Davis BR, Furberg CD, Wright JT Jr, et al. ALLHAT: setting the record straight. Ann Intern Med. 2004; 141: 39–46.
39. 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: 861-869.
40. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effects of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001; 345: 870-878.
41. Viberti G and Wheeldon NM. Microalbuminuria reduction with valsartan in patient with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation. 2002; 106: 672-678.
42. Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin dependent diabetes and hypertension. N Engl J Meed. 1998; 338: 645-52.
43. Tatti P, pahor M, Byington RP, et al. Outcome results of the Fosinopril versus Amlodipine cardiovascular events Randomized Trial (FACET) in patients with hypertension and NIDDM. Diabetes care. 1998; 21: 597-603.
44. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet. 2000; 355: 865–872.
45. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. Am J Kidney Dis. 2000; 36: 646–661.
46. British National Formulary. BNF 57, jointly published by BMJ Group and RPS Publishing, London. March 2009: 98-99. ISBN- 9780853698456.