

## Management of diabetic hypertensives

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### ABSTRACT

Hypertension occurs twice as commonly in diabetics than in comparable nondiabetics. Patients with both disorders have a markedly higher risk for premature microvascular and macrovascular complications. Aggressive control of blood pressure (BP) reduces both micro- and macrovascular complications. In diabetic hypertensives, angiotensin converting enzyme inhibitors (ACEIs) are the first line in management of hypertension, and can be replaced by angiotensin II receptor blockers (ARBs) if patients are intolerant of them. Recent studies suggest ARBs to be on par with ACEI in reducing both macro- and microvascular risks. Adding both these agents may have a beneficial effect on proteinuria, but no extra macrovascular risk reduction. Thiazides can also be used as first line drugs, but are better used along with ACEI/ARBs. Beta-blockers [especially if the patient has coronary artery disease] and calcium channel blockers are used as second line add-on drugs. Multidrug regimens are commonly needed in diabetic hypertensives. Achieving the target BP of <130/80 is the priority rather than the drug combination used in order to arrest and prevent the progression of macro- and microvascular complications in diabetic hypertensives.

**Key words:** Angiotensin converting enzyme inhibitor, angiotensin II receptor blockers, diabetes mellitus, hypertension, life-style modification

### INTRODUCTION

Hypertension and diabetes are becoming increasingly common. Hypertension occurs more commonly in diabetics than in comparable nondiabetics. Hypertension (defined as a blood pressure [BP]  $\geq 140/90$  mmHg) affects 20 to 60% of patients with diabetes, depending on obesity, ethnicity, and age.<sup>[1-3]</sup> Overall, hypertension is disproportionately higher in diabetics,<sup>[4]</sup> while persons with elevated BP are two and a half times more likely to develop diabetes within 5 years.<sup>[5,6]</sup> In India, about 50% of diabetics have hypertension.<sup>[7,8]</sup>

Most patients with both disorders have a markedly worsened risk for premature microvascular and macrovascular complications. The presence of hypertension causes a 7.2-fold increase and a 37-fold increase in mortality in diabetic patients.<sup>[9-11]</sup>

In the U.K. Prospective Diabetes Study (UKPDS) epidemiological study, each 10-mmHg decrease in mean systolic BP was associated with reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications.<sup>[12]</sup>

There is no threshold value for BP, and risk continues to decrease well into the normal range. Achieving lower levels, however, would increase the cost of care as well as drug side effects and is often difficult in practice. Therefore, a target BP goal of <130/80 mmHg is reasonable if it can be safely achieved.

Hence, aggressive BP control becomes imperative in diabetic patients.

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## ADVANTAGES OF TREATING HYPERTENSION IN DIABETICS

UKPDS and Hypertension Optimum Trial (HOT) showed early treatment of BP and tight BP control lead to significant reduction in microvascular complications (retinopathy, nephropathy, neuropathy) and macrovascular complications [coronary artery disease (CAD)/stroke/peripheral vascular disease].<sup>[12-15]</sup>

The UKPD study and other UK study groups have shown that the long-term tight BP control in hypertensive patients with type 2 diabetes mellitus results in a significant reduction in all diabetes-related end points.<sup>[12,16-18]</sup>

Tight control of blood glucose only decreases the risk of microvascular complications,<sup>[19]</sup> whereas tight control of BP reduces both micro- and macrovascular complications. Also, the beneficial results also come instantaneously with the later than with the former. Tight BP control is more cost effective and easier for clinicians and patients than tight blood glucose control.

SHEP (Systolic hypertension in elderly patients), SYST-EUR (systolic hypertension Europe trial), and HOT have confirmed that reduction in cardiovascular risk was achieved with tight BP control, and, the beneficial effect was twice or thrice when the patient is a diabetic hypertensive.<sup>[20-24]</sup>

The International Diabetic Federation Consensus Guidelines have shown reduction in stroke morbidity and mortality, heart failure morbidity and mortality, reduced left ventricular hypertrophy, decrease in CAD events, and reduction in progression of renal disease including diabetic nephropathy, by tight control of hypertension in diabetics.<sup>[25]</sup>

## MANAGEMENT OF HYPERTENSION IN DIABETICS

Management of diabetic hypertensives starts with lifestyle changes (weight reduction; regular exercise; and moderation of sodium, protein, and alcohol), as well as control of hyperglycemia, dyslipidemia, and proteinuria apart from management hypertension per se. A comprehensive algorithm encompassing all the armamentarium of management is provided in Figure 1.

In the Dietary Approaches to Stop Hypertension trial (DASH), lifestyle modifications such as exercise, a diet low in sodium, saturated fat, cholesterol, and high in potassium, calcium, fiber, fruits have clearly been shown to decrease

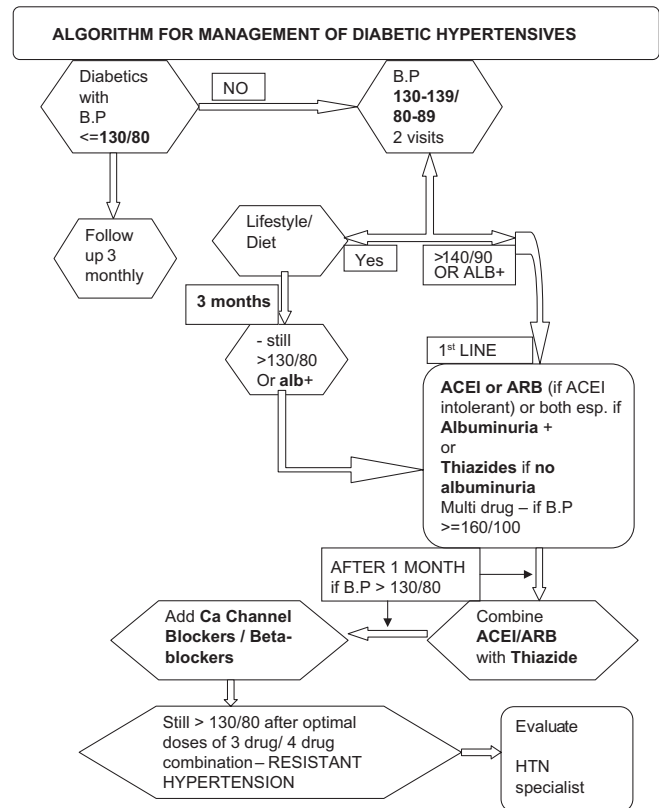


Figure 1: Algorithm for management of hypertension in diabetes

BP.<sup>[26]</sup> The DASH diet recommends keeping salt intake to less than 2 300 mg (1 500 mg a day – elderly).<sup>[27]</sup> Excessive sodium intake is particularly deleterious in patients with diabetes because it may decrease the antihypertensive effects of medications and their beneficial effects on proteinuria.<sup>[28]</sup> Also, DASH diet has beneficial effects for diabetes control and prevention of complications apart from pressure control.

The DASH study compared three eating plans: A plan that includes foods people regularly eat without intervention; a plan that includes regular food plus more fruits and vegetables alone; and the DASH eating plan, i.e., diet more in potassium, fruits, fiber, calcium and less in sodium, saturated fat, and cholesterol. All three plans included about 3 000 mg of sodium daily. Participants who followed both the plan that included more fruits and vegetables and the DASH eating plan had reduced BP, but the DASH eating plan had better control.<sup>[26]</sup>

The second DASH involved 412 participants who were randomly assigned to one of the two eating plans (DASH and REGULAR) and subdivided into three sodium intake levels (3.3 g, 2.3 g, and 1.5 g/day) and then followed for a month. Results showed that reducing dietary sodium lowered BP for both eating plans. At each sodium level,

BP was lower on the DASH eating plan than on the regular plan. The greatest BP reductions were for the DASH eating plan at the sodium intake of 1 500 mg per day.<sup>[26]</sup>

A duration of 20 to 40 minutes of aerobic exercise performed five times a week has significantly lowered BP levels.<sup>[29]</sup> It is also noted that the results of low to moderate training are just as efficient in lowering BP compared to that with high-intensity cardiovascular exercise.<sup>[30]</sup> Studies show exercise and weight reduction helps independently in reducing BP, and combining both have additive benefits in diabetic hypertensives.<sup>[31]</sup>

## DRUG MANAGEMENT OF HYPERTENSION

The choice of perfect antihypertensive remains elusive and dictated by patient's age, associated comorbidities such as chronic kidney disease (CKD), CAD, state of diabetes and hypertension, and other factors. Clinical trials with diuretics, angiotensin converting enzyme inhibitors (ACEIs), beta blockers, angiotensin II receptor blockers (ARBs), and calcium antagonists have demonstrated benefit in the treatment of diabetic hypertensives.<sup>[24,32-34]</sup>

ACEI are the first line in management of diabetic hypertensives. ACEIs may be used alone for BP lowering but are much more effective when combined with a thiazide-type diuretic or other antihypertensive drug.<sup>[35-38]</sup> They reduce the macrovascular and microvascular risks associated with diabetic hypertensives.

1. Macrovascular risks: In the subanalysis of the HOPE Study, which included both hypertensive and normotensive individuals, high-risk diabetic patients treated with ACEI added on to conventional therapy showed a reduction in all macrovascular complications (combined myocardial infarction, stroke, and cardiovascular disease (CVD) death reduction of about 25% and of stroke by about 33%) compared with placebo plus conventional therapy.<sup>[32,39-41]</sup> Earlier studies did not prove the effectiveness of ARBs in cardiovascular risk reduction, as a replacement to ACEI intolerance. ONTARGET (largest and the first ARB-based outcome study) conducted in a broad cross-section of patients at high risk of cardiovascular disease has recently showed the cardiovascular benefit of ARB be on par with ACEI. ONTARGET showed that the ARB telmisartan was as effective as the reference standard ACE inhibitor ramipril in reducing macrovascular complications (death from cardiovascular causes, myocardial infarction, stroke, and hospitalization for heart failure). ONTARGET also showed that the combination of telmisartan with ramipril did not have additional cardiac risk reduction benefit.<sup>[39,42,43]</sup>

2. The American Diabetes Association (ADA) has recommended both ACEIs and ARBs for use in type 2 diabetic patients with CKD and other microvascular complications, because these agents delay the deterioration in glomerular filtration rate (GFR) and the worsening of albuminuria.<sup>[32,40,44]</sup> Unlike macrovascular risk reduction, microvascular risks reduction is found to be more on combining ACEI and ARBs, rather than using them alone. CALM and LORD study explains the benefit of combination of these two agents in reducing microalbuminuria.<sup>[45,46]</sup>

The ADA has recommended ACEIs for diabetic patients >55 years of age at high risk for CVD and Beta-blockers for those with known CAD as first-line agents.<sup>[32]</sup>

Beta 1 selective beta-blockers are beneficial to diabetics as part of multidrug therapy, have little adverse effects such as hypoglycemic unawareness and decreased sensitivity than the nonselective counterparts. Beta-blockers value as monotherapy is less clear. A beta blocker indicated in a diabetic with ischemic heart disease is less effective in preventing stroke than an ARB, as was found in the LIFE study.<sup>[47]</sup>

In diuretic-based therapy, a low-dose thiazide diuretic, has been shown to reduce the cardiovascular event rate 34% compared with placebo; the absolute risk reduction was twice as great for diabetic subjects vs nondiabetic subjects.<sup>[48]</sup>

Calcium channel blockers may be useful to diabetics, particularly as part of combination therapy, to control BP. They were shown to reduce CVD events in diabetics compared with placebo in several clinical outcome trials.<sup>[22,27,48]</sup>

The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial in diabetics found that the nitrendipine was inferior to lisinopril in reducing the incidence of ischemic cardiac events.<sup>[50]</sup> However, in normotensive diabetics in the ABCD2 Trial, nitrendipine was equivalent to lisinopril in stroke prevention and in retardation of the development of albuminuria.<sup>[51]</sup> This explains the superiority of ACEI over the calcium channel blockers in diabetic hypertensives.

In patients with renal insufficiency, no creatinine level is an absolute contraindication to angiotensin blockade therapy (ACEI/ARB). ACE inhibitors are not nephrotoxic. ACE inhibitors are renoprotective even for levels of renal function between 10 and 30 ml/min, indicating the need not to withhold ACE inhibitors, even when GFR approximates levels requiring replacement therapy.<sup>[52]</sup> Nevertheless, careful monitoring is needed while

administering ACE inhibitors/ARB when serum creatinine levels are above 3.0 mg/dl due to fear of hyperkalemia and rapid decline in renal function in patients with advanced renal insufficiency.<sup>[53]</sup>

Treatment of hypertension in both type 1 and 2 diabetics does not vary much. Nevertheless, few preferences can be mentioned from various studies. In hypertensive type 1 diabetic patients with any degree of albuminuria (micro- and macroalbuminuria), ACE inhibitors have been preferably shown to delay the progression of nephropathy. In hypertensive type 2 diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown equally to delay the progression to macroalbuminuria. In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dl), ARBs have been preferably shown to delay the progression of nephropathy.<sup>[54-57]</sup>

Hence, while treating diabetic hypertensives, first-line agents used must be an ACEI or ARB (if intolerant to ACEI) or a combination of both or a thiazide diuretic. If the target BP goal is not obtained with the initial doses of first-line drugs, increases in doses are recommended, or the addition of a second-line drug must be considered. Regardless of the initial treatment, it must be emphasized that most patients will require more than one drug to achieve the recommended target of  $\leq 130/80$  mmHg, and many will require three or more. Add-on drugs can be calcium channel blockers (preferably dihydropyridine calcium channel blockers [DCCB group], B1 Selective beta-blockers, or alpha-blockers. Achievement of the target BP may be more important than the particular drug regimen used.

From various studies and guidelines, the following are observed:<sup>[58,59]</sup>

In diabetic hypertensives

1. Goal (mmHg) for BP -  $<130/80$  mmHg
2. Behavioral therapy alone (maximum 3 months), then add pharmacologic treatment – if -  $130-139/80-89$  mmHg
3. Behavioral therapy + pharmacologic treatment – if  $\geq 140/\geq 90$  mmHg

## GUIDELINES FOR MANAGING DIABETIC HYPERTENSIVES

- A. The target BP should be below  $130/80$  mm Hg.
- B. All routinely used antihypertensive drugs have been shown to be beneficial compared with placebo.
- C. More than one drug will usually be required to achieve the target BP.

- D. Patients with prehypertension ( $130-139/80-89$  mmHg) should be given lifestyle/behavioral therapy alone for a maximum of 3 months and then, if targets are not achieved, should also be treated pharmacologically. Attention should be paid to lifestyle changes (weight reduction; regular exercise; and moderation of sodium, protein, and alcohol), as well as control of hyperglycemia, dyslipidemia, and proteinuria, for all the patients.
- E. The choice of drugs should always include an ACE inhibitor (or an angiotensin II receptor blocker, if ACE inhibitors cannot be tolerated) and should usually include a diuretic. If additional therapy is needed, a calcium-channel blocker,  $\beta$ -blocker, or  $\alpha$ -blocker may be used [Figure 1].

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