ABSTRACT
Untreated or poorly controlled hypertension can significantly accelerate the development and progression of both the micro and macrovascular complications of diabetes. Aggressive blood pressure control improves patient outcomes and reduces health care costs. Unfortunately, nearly two-thirds of people with diabetes do not have blood pressure readings within the target range. Effective antihypertensive regimens maximize nonpharmacological therapies, minimize adverse effects on glucose control, lessen the risk of medication-related side-effects, and provide adequate cardiac and renal protection. Early improvement in blood-pressure control in patients with both type 2 diabetes and hypertension is associated with a reduced risk of complications, but good blood-pressure control must be continued if the benefits are to be maintained.

INTRODUCTION
Hypertension was defined as sustained elevation in blood pressure \( \geq 140/90 \text{ mm Hg} \). However, the new definition proposed by the Writing Group of American Society for Hypertension (WG-ASH) describes it as a complex cardiovascular disorder rather than just blood pressure values. It characterizes the disease as a progressive cardiovascular syndrome with many causes that result in both functional and structural changes in the heart and vascular system. The new definition incorporates the presence or absence of risk factors, early disease markers, target-organ damage and different physiologic abnormalities in the cardiovascular system and other organs caused by hypertension. Though initially symptomless, it is deadly since uncontrolled hypertension can lead to target organ damage & thus multiple adverse clinical outcomes including stroke, heart failure or kidney failure. Thus it is rightly labelled as the “silent killer.”

Hypertension is a triple paradox: easy to diagnose but often remains undetected; simple to treat but often remains untreated; despite availability of drugs, treatment is not adequately effective. Statistics reveal that many of the patients with hypertension do not have their blood pressure under control.

High blood pressure is the biggest single cause of death worldwide through heart attack, stroke and kidney diseases. The situation is graver in our country since with modernization, we are trading healthy traditional diets for fatty foods, physical jobs for desk bound ones and calm rural life for stressful city life. Thus, after being referred to as the Diabetes Capital, India is also slated to become the “Hypertension Capital”.

According to a recent review on “The Global Burden of Hypertension”, the estimated prevalence of hypertension (in people aged 20 years and older) in India in 2000 was 20.6% among males and 20.9% among females and is projected to increase to 22.9% and 23.6% respectively in 2025.

Hypertension in diabetics: The deadly combination
The prevalence of hypertension in the diabetic population is 1.5-3 times higher than that of nondiabetic age-matched groups. Compared to patients without diabetes, hypertension is characterised by an earlier onset of systolic hypertension and ISH is also more prevalent at any age. The co-existence of hypertension and type 2 diabetes is more common in women and the systolic BP is steeper in women.

The timing and presentation of hypertension differs between type 1 and type 2 diabetes. In type 1 diabetes, hypertension develops after several years of the disease and usually reflects the development of diabetic nephropathy. It ultimately affects 30% of individuals with type 1 diabetes. In type 2 diabetes, hypertension may be present at the time of diagnosis or even before the development of hyperglycemia. Several confounding factors are present in type 2 diabetes that makes the assessment of the prevalence of hypertension attributable to diabetes difficult. Type 2 diabetic patients are older and have a greater degree of adiposity than nondiabetic patients. The prevalence of hypertension in Western populations increases with age and degree of obesity. Elevated blood pressure in these individuals may represent the aging or obesity of the population. However, after adjusting for age and weight, the prevalence of hypertension is still 1.5 times higher in diabetic groups. Approximately 20-60% of patients with type 2 diabetes will develop hypertension, depending on age, ethnicity, and obesity. In some ethnic groups, diabetic nephropathy may be the primary determinant of hypertension in type 2 diabetes. This has been documented in Pima Indians. The clustering of hypertension, glucose intolerance or frank type 2 diabetes, hyperlipidemia, central obesity, and insulin resistance has been documented in
several populations including Indians. Extensive epidemiological evidence indicates that diabetic individuals with hypertension have greatly increased risks of cardiovascular disease, renal insufficiency, and diabetic retinopathy. The relationship between diabetic neuropathy and arterial hypertension is less clear. However, some epidemiological studies suggest that hypertension may be a contributory factor for this condition as well.

Complications of Hypertension in Diabetes
Along with hyperglycemia, dyslipidemia, and cigarette smoking, hypertension is a major contributor to the development and progression of macrovascular and microvascular complications in people with diabetes. Compared to the general population, people with diabetes face a two to fourfold increased risk of cardiovascular disease (CVD). Concomitant hypertension triples the already high risk of coronary artery disease (CAD), doubles total mortality and stroke risk, and may be responsible for up to 75% of all CVD events in people with diabetes. Similarly, hypertension significantly accelerates the progression of diabetic nephropathy, retinopathy, and neuropathy. Of particular importance, systolic blood pressure is a stronger predictor than diastolic blood pressure for both CVD and renal complications.

Treatment of Hypertension in Diabetes: The goal
How far should blood pressure be lowered in people with diabetes? There is a continuous relationship between the level of blood pressure and the risk of complications. Starting at 115/75 mm Hg, CVD risk doubles with each increment of 20/10 mm Hg throughout the blood pressure range. Reducing blood pressure in people with hypertension and diabetes decreases both macrovascular and microvascular complications. Clinical trials using a variety of antihypertensive agents have demonstrated that even modest reductions in blood pressure of just 9–11 mmHg systolic and 2–9 mmHg diastolic decrease CVD events by 34–69% and microvascular complications (retinopathy and nephropathy) by 26–46% within just 2–5 years.

Randomized clinical trials have demonstrated substantially improved CVD and microvascular outcomes with a target diastolic blood pressure close to or < 80 mmHg. For the prognostically more important systolic blood pressure randomized clinical trial and prospective observational data from other clinical trials support improved CVD and microvascular outcomes with a target systolic blood pressure < 130 mmHg. Based on these data, most international guidelines now recommend a target blood pressure of < 130/80 mmHg for people with diabetes.

For diabetic patients with proteinuria and a total urinary protein-to-creatinine ratio > 500 mg/g, the National Kidney Foundation recommends a target systolic blood pressure < 125 mmHg. Limited data suggest possible worsening of both renal and CVD outcomes if systolic blood pressure is lowered to < 110 mmHg. Epidemiologic analyses show that blood pressures >115/75 mmHg are associated with increased cardiovascular event rates and mortality in individuals with diabetes. The ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is designed to determine whether lowering systolic blood pressure to <120 mmHg provides greater cardiovascular protection than a systolic blood pressure level of <140 mmHg in patients with type 2 diabetes.

Intensive blood pressure control is an essential component of a multifactorial strategy to reduce CVD and microvascular complications in diabetes. The Steno 2 study targeted intensive goals for hypertension, hyperglycemia, and dyslipidemia in patients with type 2 diabetes and microalbuminuria. After 8 years, the combined interventions reduced CVD events by 53% and major microvascular complications by 58–63%. An economic modeling study based on clinical trial data has suggested that intensive hypertension control in diabetes is actually cost-saving; it improves health outcomes and reduces total health care costs. In contrast, intensive glycemic and dyslipidemia control are only cost-effective; they improve health outcomes but result in some increase in health care costs.

GOAL: B.P.
1. Hypertension without co-morbidity < 140/90 mm Hg
2. Diabetes Mellitus: < 130 / 80 mm Hg
3. Congestive Heart Failure: < 130/80 mm Hg
4. Renal Insufficiency: < 130 / 80 mm Hg
5. Patients with proteinuria and a total urinary protein-to-creatinine ratio > 500 mg/g < 125 / 75 mm Hg

STATUS OF CONTROL OF HYPERTENSION IN DIABETES
Unfortunately, outside of research settings, control of vascular risk factors is inadequate in people with diabetes. In community-based studies, only 28–36% of diabetic hypertensive patients have their blood pressure controlled to < 130/80 mmHg, primarily because of poor control of systolic blood pressure. Similar levels of inadequate blood pressure control have been noted in type 1 diabetic populations. Of great concern, only 4–10% of diabetic patients meet the combined American Diabetes Association goals for blood pressure (< 130/80 mmHg), LDL cholesterol (< 100 mg/dl), and hemoglobin A1c (< 7.0%). In community settings, patients with diabetes are less likely to have their blood pressure controlled, despite receiving more antihypertensive medications.

Disease, patient, and clinician factors contribute to poor blood pressure control in diabetes. Hypertension, particularly elevated systolic blood pressure, may be intrinsically more difficult to control in the diabetic population. Clinician inertia—the failure to increase the dose or number of medications at office visits for patients who are not meeting therapeutic goals is an important contributor to poor control of blood pressure. Inadequate knowledge of control of hypertension as the most cost-effective intervention to prevent CVD may be another reason and time pressure during short office visits with complicated patients with
Management of Hypertension in Diabetes

**TREATMENT STRATEGIES**

The basic paradigm for achieving blood pressure goals in people with diabetes has not changed appreciably from that recommended by JNC 7.19 However, physicians should adopt a more integrated, patient-centered management of hypertension, especially in diabetics by treating the intricacies of each patient profile including their total CVD risk rather than focusing on the disease in isolation.

Although there are no well-controlled studies of lifestyle changes in the treatment of hypertension in individuals with diabetes, studies in nondiabetic individuals have shown antihypertensive effects similar to pharmacologic monotherapy of limiting salt intake to <2.4 g/day; weight reduction; adopting the Dietary Approaches to Stop Hypertension (DASH) eating plan (increasing consumption of fruits, vegetables, and low-fat dairy products); avoiding excessive alcohol consumption; and engaging in yoga, physical activities and smoking cessation.40 These nonpharmacological strategies may also positively affect glycemia and lipid control. Their effects on cardiovascular events have been found to be beneficial. All patients should be counseled regarding life style modifications. An initial trial of nonpharmacologic therapy may be reasonable in diabetic individuals with mild hypertension (systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg) for 3 months and then, if targets are not achieved, be treated with addition of pharmacological agents.

Given the modest efficacy of lifestyle modifications and the importance of prompt blood pressure control, diabetic hypertensive patients with blood pressure ≥140/90 mmHg or with albuminuria or other Target Organ Damage (TOD) should initiate pharmacological therapy concurrently with lifestyle modification at the second office visit. Lifestyle modification should be reemphasized at each office visit.

Patients with more severe hypertension (blood pressure ≥140/≥90 mmHg) at diagnosis or follow-up should receive pharmacologic therapy in addition to lifestyle therapy.28

**PHARMACOLOGICAL TREATMENT OF HYPERTENSION IN DIABETES**

Clinical trials including large numbers of patients with both diabetes and hypertension have demonstrated reductions in CVD events and microvascular complications, using thiazide diuretics, ACE inhibitors, angiotensin receptor blockers (ARBs), dihydropyridine (DHP) and nondihydropyridine (non DHP) calcium channel blockers (CCBs), and β-blockers.11-18 More recent randomized studies in subjects with diabetes have investigated whether any particular antihypertensive agent more effectively reduces either CVD or renal complications independently of its ability to lower blood pressure.12,24-44

Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted. If needed to achieve blood pressure targets, a thiazide diuretic should be added to those with an estimated glomerular filtration rate (GFR) ≥50 ml/min per 1.73 m² and a loop diuretic for those with an estimated GFR <50 ml/min per 1.73 m². Multiple drug therapy (two or more agents at maximal doses) is generally required to achieve blood pressure targets. We may like to add drugs such as aldosterone receptor blockers (particularly recommended in patients with diabetes and obesity), a different subclass of CCBs, or alpha-blockers. Addition of the well established effect of another RAS blocker (direct renin inhibitors) on interaction of renin/prorenin with its receptor may be potentially useful. In patients with diabetes mellitus as a second drug or in combination with other drugs. DRI has been found to be cardio and Reno protective in recent trials. If ACE inhibitors, ARBs, or diuretics are used, kidney function and serum potassium levels should be closely monitored.

Most diabetic hypertensive patients with normal renal function require a combination of two to three antihypertensive agents to lower blood pressure to target level of <130/80 mmHg; patients with concomitant chronic kidney disease may require three or more agents.12,18

Initial treatment in patients with blood pressure ≥20 mmHg above goal should be started on treatment with a once-daily renin-angiotensin system (RAS) blocker (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]). In a recent trial Irbesartan has been found to be renoprotective independently of its blood-pressure–lowering effect in patients with type 2 diabetes and microalbuminuria A thiazide-like diuretic or a calcium channel blocker (CCB) or vasodilating beta-blocker should be added if blood pressure remains >20/10 mmHg above goal after 1 month of RAS inhibitor treatment, including uptitrating to maximal dose. A loop diuretic should be substituted in patients with an estimated glomerular filtration rate of <50mL/min. For the individual patient, issues of quality of life (for example, impotence with diuretics and β-blockers) might be decisive. Nonetheless, β-blockers are preferred in post infarct patients or in those with heart failure or unstable angina (a contraindication to dihydropyridines in the absence of β-blockade).

<table>
<thead>
<tr>
<th>Modification</th>
<th>Potential Reduction in Systolic/Diastolic Blood Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10–lb weight loss</td>
<td>7/6</td>
</tr>
<tr>
<td>American Heart Association</td>
<td>11.4/5.5</td>
</tr>
<tr>
<td>Dietary Approaches to Stop Hypertension diet</td>
<td>3.9/2.4</td>
</tr>
<tr>
<td>Restriction of alcohol consumption</td>
<td>3.4/1.9</td>
</tr>
<tr>
<td>Men ≤ 2 drinks / day</td>
<td>2.4 g/day</td>
</tr>
<tr>
<td>Women ≤ 1 drink /day</td>
<td>2.4 g/day</td>
</tr>
</tbody>
</table>

**Table 1: Lifestyle Modification to Lower Blood Pressure**

The importance of prompt blood pressure control, diabetic hypertensive patients with blood pressure ≥140/90 mmHg or albuminuria or other Target Organ Damage (TOD) should initiate pharmacological therapy concurrently with lifestyle modification at the second office visit.
An important caveat is that most patients with hypertension require multi drug therapy to reach treatment goals, especially diabetic patients whose targets are lower. Many patients will require three or more drugs to reach target goals\(^2\). In ACC meeting 2009 data on Polypill was presented. 412 patients received Polypill, with \textit{hydrochlorothiazide} 12.5 mg, \textit{atenolol} 50 mg, \textit{ramipril} 5 mg, simvastatin 20 mg and \textit{aspirin} 100 mg for 12 weeks with appropriate lifestyle modification. It was reported that the polypill lowered blood pressure similar to the added effects of each of its three BP-lowering components, with an average reduction of 7 mm Hg systolic, with no interference of aspirin with the BP-lowering effects. Heart rate (an indicator of beta blockade) and urinary \textit{11-dehydrothromboxane B2}--a measure of aspirin effectiveness--were also lowered to a similar degree with the polypill as with the individual components. However it was further stated that this strategy did not prolong survival or reduce stroke, heart attack, heart failure, or kidney failure, they noted. “More trials are needed”. As reported at the ACC 2009 meeting, the calcium channel blocker combination reduced the combined rate of cardiovascular death, MI, stroke, hospitalization for unstable angina, and revascularization at 39 months by 20% compared with the diuretic-based combination.

The current review of ACE inhibitors (and ARBs) is also a reminder that physicians should consider adding another medication prior to prescribing the full dose of these drugs. With these principles in mind, both physician and patient will get the maximum benefit from the chosen antihypertensive regimen. Fixed-dose antihypertensive drug combinations may improve patient adherence as well as effectiveness in lowering blood pressure. More recently, the ACCOMPLISH trial provided overwhelming evidence that a combination of benazepril (ACE inhibitor) and amlodipine (calcium antagonist) was superior to a fixed combination of benazepril and hydrochlorothiazide in nondiabetic and diabetic patients, in spite of similar blood pressure reduction\(^6\). The results resemble the benefit that was achieved with a similar ACE inhibitor/calcium antagonist therapy in the ASCOT trial\(^4\).

Because these patients are at such high cardiovascular risk, they require an integrated intervention that also includes optimal achievement of goals for glycemic control (glycated hemoglobin [HbA1c] <7% and preprandial capillary plasma glucose 70-130 mg/dL, lipid levels, and inhibition of platelet aggregation (therapy with low-dose aspirin 75-162mg/day). All diabetes patients should be on a statin, with other drugs added, if necessary, to achieve levels of low-density lipoprotein cholesterol <70mg/dL, triglycerides <150mg/dL and high-density lipoprotein cholesterol >40 mg/dL in men and >45 mg/dL in women. Potassium levels should be kept to <5mEq/L, with lifestyle interventions or adjustment of therapy, as this may reduce cardiovascular risk.

During pregnancy in diabetic women with chronic hypertension, target blood pressure goals of systolic blood pressure 110–129 mmHg and diastolic blood pressure 65–79 mmHg are reasonable, as they contribute to long-term maternal health. Lower blood pressure levels may be associated with impaired fetal growth. During pregnancy, treatment with ACE inhibitors and ARBs is contraindicated, since they are likely to cause fetal damage. Antihypertensive drugs known to be effective and safe in pregnancy include methyldopa, labetalol, diltiazem, clonidine, and prazosin. Chronic diuretic use during pregnancy has been associated with restricted maternal plasma volume, which might reduce uteroplacental perfusion\(^4\).

**CONCLUSIONS**

All patients with diabetes should have routine blood pressure measurements at each scheduled diabetes follow-up visit. Diabetic patients with blood pressures >130 mmHg systolic or >80 mmHg diastolic are candidates for antihypertensive treatment aimed at lowering blood pressure to <130/80 mmHg. Before beginning treatment, patients with elevated blood pressures should have their blood pressure reexamined within 1 month to confirm the presence of hypertension. In patients with blood pressures between 130/80 and 140/90 mmHg, a life style modification may be used for at least 3 months. If after a trial period of lifestyle modification blood pressure remains >130 mmHg systolic or >80 mmHg diastolic, pharmacological treatment should be added.

Patients with confirmed blood pressures of 140/90 mmHg are candidates for immediate pharmacological treatment in addition to behavioral treatment. Initial drugs for pharmacological treatment include ACE inhibitors, ARBs, low-dose thiazide diuretics, and \(\beta\)-blockers. Because of the large number of studies in patients with diabetes demonstrating improvement in a range of outcomes, including progression of nephropathy, cardiovascular events, and mortality, it is now an established practice to begin hypertensive patients with diabetes and without microalbuminuria on an ACE inhibitor. When microalbuminuria or more advanced stages of nephropathy is present, ACE inhibitors (type 1 diabetes) and ARBs (type 2 diabetes) have been found to be effective in preventing the progression of nephropathy. However, cardiovascular data are limited with ARBs. Although the evidence is not complete, this is certainly a reasonable strategy, as is initial therapy with a \(\beta\)-blocker, unless contraindicated, because the UKPDS study showed \(\beta\)-blockers to be roughly equivalent to ACE inhibitors in improving multiple diabetes-related end points.

If the target blood pressure goal 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 be emphasized that most patients will require more than one drug to achieve the recommended target of <=130/80 mmHg, and many will require three or more. Achievement of the target blood pressure may be more important than the particular drug regimen used.

Thiazide diuretics have been shown to improve cardiovascular outcomes and may address the volume or salt-sensitive components of hypertension, complementing the mechanisms of action of other drugs, so these are appropriate choices for a
second or third drug and can be used for initial therapy in patients without additional cardiovascular risk factors or proteinuria.

NDCCBs can be used when ACE inhibitors, ARBs, or β-blockers are not tolerated or are contraindicated or when a second or third drug is required. There is some evidence that NDCCBs are not as effective in preventing complications, particularly myocardial infarction, heart failure, and nephropathy. However, in studies achieving low-targeted blood pressures with substantial improvements in outcomes, such as the HOT study and the UKPDS, DCCBs were commonly part of an effective multi-drug regimen that also included an ACE inhibitor or a β-blocker, often with a diuretic.

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 are specific indications for their use apart from treatment of hypertension (for example, alpha-blockers for patients with benign prostatic hypertrophy and diltiazem for rate control in atrial fibrillation), or when additional drugs are required to achieve the target for blood pressure.

In diabetic patients >65 years of age with isolated systolic hypertension (i.e., >140 mmHg systolic and <80 mmHg diastolic blood pressure), pharmacological treatment should be initiated. Earlier recommendations to treat to a systolic blood pressure <160 have been reduced in order to be consistent with JNC Report and are based on the increased cardiovascular risk of these patients and the results of the Systolic Hypertension in Elderly Program study, in which a systolic blood pressure of 144 was achieved. Combinations of agents are often required. When drug therapy is intensified, patients should be monitored carefully for adverse effects, such as orthostatic hypotension. Finally, it is important to note that in diabetic patients the greatest reduction in cardiovascular mortality occurs at a diastolic blood pressure of 80 mmHg. Thus, aggressive blood pressure control should be attempted in all diabetic patients.

Treatment decisions should, of course, be individualized based on the clinical characteristics of the patient, including comorbidities as well as tolerability, personal preference, and cost, especially for patients who must pay out of pocket for medications. Fixed-dose combinations of many drugs are available and may help with compliance and be less expensive for patients with a prescription co-payment.

REFERENCES:


45. Jamerson KA: Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension Trial (ACCOMPLISH): the first hypertension trial comparing the effects of two fixed-dose combination therapy regimens on cardiovascular events. J Clin Hypertens (Greenwich) 2003; 5 (Suppl 3): 29–35CrossRefMedline


