Chapter 31
Hypertension

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Introduction

Hypertension is a major risk factor for cardiovascular disease (CVD). It substantially increases the risk for coronary heart disease (CHD), stroke, and nephropathy. There is a positive association between hypertension and insulin resistance and the evidence of a causal link is growing. When hypertension coexists with diabetes, as it commonly does, the risk of stroke or CVD is doubled and the risk for developing end-stage renal disease increases to 5–6 times, compared to hypertensive patients without diabetes. In this chapter we discuss the interaction of hypertension, insulin resistance, and other CVD risk factors in the context of the metabolic syndrome, emphasizing the unique aspects of hypertension in patients with diabetes. Therapy for hypertension is discussed in the light of the major prospective trials available to date, such as the HOPE, RENAAL, IDNT, and IRMA.

Hypertension and CVD in Patients with Diabetes

CVD is the major cause of mortality in patients with diabetes. Risk factors for CVD that cluster with diabetes (Table 31.1) include hypertension, central obesity, dyslipidemia, microalbuminuria, and coagulation abnormalities.[1]

Among these risk factors, hypertension is approximately twice as frequent in patients with diabetes compared to those without the disease and accounts for up to 75% of CVD risk. Conversely, patients with hypertension are more likely to have diabetes than are normotensive persons.[2] In a prospective study of 12,550 adults, the development of type 2 diabetes was nearly 2.5 times as frequent in patients with hypertension as in their normotensive counterparts after adjustment for age, sex, race, education, adiposity, family history of diabetes, physical activity, and other health-related behavior.[3]

The association of hypertension, insulin resistance, and the resultant hyperinsulinemia was shown in several studies. In untreated essential hypertensive patients, fasting and postprandial insulin levels were higher than in normotensive controls, regardless of body mass index (BMI), and plasma insulin correlated directly with blood pressure (BP), suggesting that essential hypertension is an insulin-resistant state.[4] Another study of 24 adults documented that those with hypertension, whether treated or untreated, were insulin resistant, hyperglycemic, and hyperinsulinemic compared to a well-matched control group.[5] Insulin resistance and hyperinsulinemia also exist in rats with genetic hypertension such as Dahl hypertensive and spontaneously hypertensive rat (SHR) strains.[6,7] In contrast, the absence of an association between insulin resistance and essential hypertension in secondary hypertension[8] suggests a common genetic predisposition for essential hypertension and insulin resistance, a concept that is also supported by the finding of altered glucose metabolism in normotensive offspring

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Table 31.1 CVD risk factors associated with diabetes

1. Hypertension
2. Obesity
3. Hyperinsulinemia/insulin resistance
4. Endothelial dysfunction
5. Microalbuminuria
6. Low HDL cholesterol levels
7. High triglyceride levels
8. Small, dense LDL cholesterol particles
9. Increased apo-lipoprotein B levels
10. Increased fibrinogen levels
11. Increased plasma activator inhibitor-1 levels
12. Increased C-reactive protein and other inflammatory markers
13. Absent nocturnal dipping of blood pressure and pulse
14. Salt sensitivity
15. Left ventricular hypertrophy
16. Premature coronary artery disease

of hypertensive patients.[9,10] Therefore, hypertension in patients with diabetes must be viewed in the context of the metabolic syndrome. This has important implications in understanding the principles of management of these patients as discussed later. Detailed discussion of the metabolic syndrome (Syndrome X) is presented in Chapter 43.

Unique Aspects of Hypertension in Patients with Diabetes

Hypertension in patients with diabetes has unique features, such as increased salt sensitivity, volume expansion, isolated systolic BP elevation, loss of nocturnal dipping of BP and pulse, increased propensity to proteinuria, and orthostatic hypotension.[2] Most of these features are considered risk factors for CVD (Table 31.1) and are relevant to the selection of appropriate antihypertensive medications, for example, low-dose diuretics to reduce volume expansion, and angiotensin-converting enzyme inhibitors (ACEs) or angiotensin receptor blockers (ARBs) to minimize proteinuria.

Salt Sensitivity and Volume Expansion

Alterations in sodium balance and extracellular fluid volume have varying effects on BP in both normotensive and hypertensive subjects. The rise of BP in response to dietary salt intake is greatest in hypertensive African-American and elderly patients who have diabetes, obesity, renal insufficiency, and low plasma renin activity. Similarly, salt sensitivity in normotensive subjects is also associated with a greater age-related increase in BP. Thus, in the management of hypertension in patients with diabetes, age is especially important among the factors affecting salt sensitivity, since the prevalence of both diabetes and salt sensitivity increases in the elderly.

Isolated Systolic Hypertension

The earlier onset and accelerated progression of atherosclerosis in patients with diabetes leads to the loss of elasticity and the "cushioning" effect in larger arteries, causing an increase in systolic BP. The more rapid runoff of blood during the systolic ejection phase of the cardiac cycle results in a lower diastolic BP, producing a widened pulse pressure and isolated systolic hypertension, which is more common and occurs at a relatively younger age in patients with diabetes.[2]

Loss of Nocturnal Decline of BP

In normotensive individuals, BP shows a reproducible circadian pattern during 24-h ambulatory monitoring. BP is highest during daytime hours and typically falls by 10–15% during sleep, a pattern termed nocturnal "dipping." A nocturnal decline in BP <10% compared to daytime BP values (non-dipping)[11] has been observed in patients with diabetes. The loss of nocturnal dipping increases risk for stroke and myocardial infarction and is consistent with data showing the superiority of ambulatory BP compared to office BP in predicting target organ involvement, such as left ventricular hypertrophy.[11] Since about 30% of myocardial infarctions and 50% of strokes occur between 6:00 AM and noon it is mandatory to design dosing strategies which use antihypertensive medications that provide consistent, sustained 24 h BP control.[12]

Microalbuminuria

There is considerable evidence that hypertension in type 1 diabetes is a consequence, rather than a cause, of renal disease and that nephropathy precedes the rise in BP.[2] Persistent hypertension in patients with type 1 diabetes is often a manifestation of diabetic nephropathy as indicated by concomitant elevation of urinary albumin. Both hypertension and nephropathy appear to exacerbate each other. In type 2 diabetes, microalbuminuria is correlated with insulin resistance,[13] salt sensitivity, loss of nocturnal dipping, and left ventricular hypertrophy.[14] Elevated systolic BP is a significant determining factor in the progression of microalbuminuria. Indeed, there is increasing evidence that microalbuminuria is an integral component of the metabolic syndrome associated with hypertension.[14] Therefore, in hypertensive patients with diabetes, antihypertensive medications should have the dual effect of reducing proteinuria and lowering blood pressure as seen with the use of ACE inhibitors and ARBs. Agents which block the renin–angiotensin–aldosterone system (RAAS) have evolved as increasingly important tools in reducing the progression of nephropathy in such patients.

Orthostatic Hypotension

Pooling of blood in dependent veins during rising from a recumbent position normally leads to decrease in stroke volume and systolic BP with reflexogenic sympathetic response and resultant increases in systemic vascular resistance and heart rate. In patients with diabetes and autonomic dysfunction, excessive venous pooling can cause immediate or delayed orthostatic hypotension that might cause reduction in cerebral blood flow leading to intermittent lightheadedness, fatigue, unsteady gait, and syncope.[15] Orthostatic hypotension in patients with diabetes and concomitant hypertension has several diagnostic and therapeutic implications. For example, discontinuation of diuretic therapy and volume repletion might be necessary. Also α-adrenergic receptor blockers may be less desirable as second-line agents. In the subset of patients with "hyperadrenergic" orthostatic hypertension, manifested by excessive sweating and palpitation, the use of low-dose clonidine may blunt excess sympathetic response.[16] Finally, for patients with diabetes who are at risk for orthostatic hypertension, doses of all antihypertensive agents must be titrated more carefully.

Management of Hypertension in Patients with Diabetes

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII)[17] characterizes hypertension and concomitant diabetes as a high-risk condition and a compelling indication for specific pharmacologic therapy. The Report notes that the combined prevalence of diabetes and impaired fasting glucose in subjects over age 20 is 14.4% and that diabetes is the leading cause of blindness, end-stage renal disease, and nontraumatic amputations. Type 2 diabetes, per se, increases the likelihood of premature death from CVD or stroke by 70–80%, but with concurrent hypertension, CVD,

stroke, progression of renal disease, and retinopathy are greatly accelerated. Randomized controlled trials that have included large diabetic populations (UKPDS[18], HOT[19], SHEP[20], Syst EUR[21], HOPE[22], MICRO-HOPE[22], LIFE[23], and ALLHAT[24]) have shown improved CVD outcomes if BP was controlled to 130/80 mmHg or lower. In view of studies of chronic kidney disease in patients with diabetes, defined by albuminuria (albumin >300 μg/day or >200 μg/g creatinine in a random urine) or renal insufficiency (estimated GFR <60 mL/min, corresponding to serum creatinine >1.5 mg/dL in men and 1.3 mg/dL in women) showing that the rate of decline of renal function varies continuously with BP, down to a level of 125–130/75–80 mmHg, JNC 7 recommended a BP target <130/80 mmHg in patients with diabetes, consistent with guidelines advocated by the American Diabetes Association (ADA),[25] the National Kidney Foundation (NKF),[26] and the Canadian Hypertension Society.

The question of which class of antihypertensive agents should constitute first-line therapy is largely academic since most patients with diabetes and hypertension will require at least two agents to achieve target BP levels. Indeed, in our study of 1372 patients with hypertension and diabetes, an average of 3.1 medications was required to achieve a target BP ≤130/85 mmHg,[27] consistent with results from other major studies such as UKPDS, MDRD, HOT, and ABCD[28] mentioned above, where more than two medications were often required for optimal control of BP. Diuretics, ACE inhibitors, ARBs, beta blockers (BBs), and calcium channel blockers (CCBs) have been shown to be beneficial in treating hypertension in patients with diabetes. For patients at high-CVD risk, such as those with diabetes presenting with BP>20/10 mmHg above target, JNC 7 recommends that antihypertensive therapy should be initiated with two agents, one of which would typically be a diuretic. Low-dose combinations were found to produce BP reductions that were additive, but as doses of the components were increased, BP reduction was less than additive, even though overall BP was reduced.

The following treatment algorithm (Fig. 31.1) reflects the new treatment goal of BP <130/80 mmHg as well as the latest recommendations regarding drug therapy.[29,30]

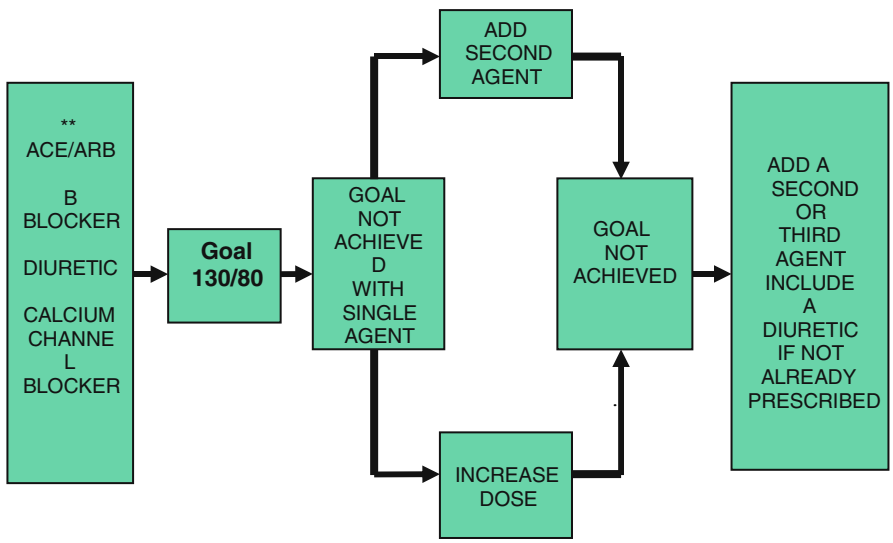

Fig. 31.1 Management of hypertension in patients with diabetes. In patients with >1 g proteinuria and renal insufficiency the treatment goal is BP <125/75 mmHg. **ARBs = angiotensin receptor blockers

Dietary and Lifestyle Modifications

Lifestyle and dietary modifications are an integral part of the management of hypertension in patients with diabetes. Attempts to modify other CVD risk factors such as smoking, inactivity, and elevated LDL cholesterol should be made.[25] Dietary and lifestyle modifications recommended for patients with hypertension are listed in Table 31.2.

Table 31.2 Dietary and lifestyle modifications recommended for management of hypertension

1. Weight loss
2. Exercise (aerobic physical activity) 30–45 min at least three times a week
3. Reduced sodium intake to 100 mmol (2.4 g) per day
4. Smoking cessation
5. Adequate intake of dietary potassium, calcium, and magnesium.
6. Reduced alcohol intake to < 1 oz of ethanol (24 oz of beer) per day.
7. Diet rich in fruits and vegetables but low in fat[a]

[a]Based on the results of the dietary approaches to stop hypertension (DASH) study,[31,32] the reduction of sodium intake to levels below the current recommendation of 100 mmol per day and the DASH diet both lower BP substantially, with greater effects in combination than each of these approaches used alone.[32]

Dietary management and exercise in patients with diabetes are discussed in detail in Chapters 41 and 42, respectively. It is important to integrate the above lifestyle and dietary modifications for hypertension in the overall nutritional and lifestyle management of these patients.

Pharmacological Therapy for Hypertension in Patients with Diabetes

Angiotensin-Converting Enzyme Inhibitor

ACE inhibitors were first introduced in the early 1980s as antihypertensive agents. Subsequently, their ability to attenuate albuminuria and renal disease progression led to their use as renoprotective agents in diabetic nephropathy.[33] More recently, randomized controlled trials have shown that ACE inhibitors provide cardiovascular and microvascular benefits and may also improve insulin resistance. These cardiovascular benefits were greater than those attributable to the decrease in blood pressure alone, and were particularly demonstrated in people with diabetes.[22] However, the beneficial effect of ACE-inhibition in preventing diabetes was not confirmed in the DREAM trial in which treatment of 5269 patients with impaired plasma fasting glucose or glucose intolerance over 3 years with the ACE inhibitors, ramipril, failed to reduce the incidence of new-onset diabetes, compared to the insulin-sensitizing agent, rosiglitazone.[34] In patients with type 1 diabetes and proteinuria, ACE inhibitor treatment was associated with a 50% reduction in the risk of the combined end points of death, dialysis, and transplantation.[33] Furthermore, ACE inhibitors provide considerable benefits in diabetic patients with heart failure. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, ACE inhibitors reduced left ventricular mass and left ventricular dilation and significantly reduced mortality and hospitalization for heart failure.[35] ACE inhibitors have also been reported to slow the progression of diabetic retinopathy.[36]

With these clearly proven benefits, ACE inhibitors form the cornerstone of therapy for patients with hypertension and diabetes, particularly for those with proteinuria as well as for those with heart failure.

Treatment with ACE inhibitors is associated with cough in a substantial minority of patients (up to 15%), probably secondary to accumulation of bradykinin or substance P in the upper airways (Fig. 31.2). Angioedema is a rare, unpredictable, and potentially life-threatening adverse effect, particularly if the upper airway is involved, and requires immediate discontinuation and supportive care, including airway protection. ACE inhibitors reduce aldosterone secretion (Fig. 31.2) and may cause hyperkalemia, especially at the initiation of therapy. Patients with diabetes and mild renal insufficiency and those on potassium-sparing diuretics are at greater risk. Aldosterone antagonists, such as spironolactone and eplerenone, should be used with caution. Concomitant use of thiazide or loop diuretics and limitation of dietary potassium intake should allow the use of ACE inhibitors without inducing hyperkalemia. In patients with normal renal function, ACE inhibitors have little effect on glomerular filtration rate (GFR), but with reduced renal function, these agents may precipitate uremia. In patients with diabetes, a decrease in GFR of up to 25% from reduced efferent arteriolar tone and decreased intraglomerular pressure may be used as an indicator of the adequacy of ACE inhibition. ACE inhibitors are relatively contraindicated in patients with known bilateral renal artery stenosis and unilateral stenosis with a solitary kidney because of the risk of renal failure.

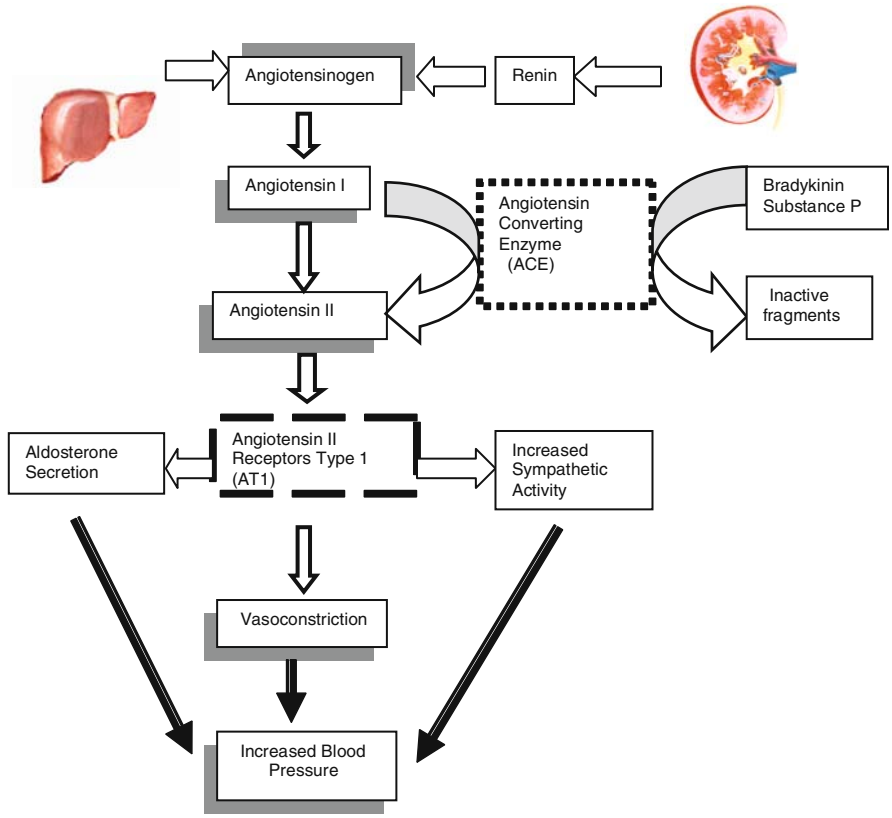

Fig. 31.2 Renin–angiotensin–aldosterone system (RAAS). Site of action for ACE inhibitors and of angiotensin receptor blockers (ARBs)

Angiotensin II Receptor Blockers

There are at least four types of angiotensin II receptors: AT1, AT2, AT3, and AT4. Of these, the AT1 receptors mediate most of the effects of angiotensin II, including vasoconstriction, cardiomyocyte and vascular smooth muscle hypertrophy, aldosterone release, increased sympathetic outflow, and stimulation of sodium reabsorption. ARBs selectively inhibit the binding of angiotensin II to the AT1 receptors; therefore, they are also called AT1 receptor blockers. Unlike ACE inhibitors, ARBs have no effects on bradykinin (Fig. 31.2) and are therefore well tolerated with a lower incidence of side effects such as cough. Angioedema may occur rarely (probably an idiosyncratic reaction), but much less commonly than with ACE inhibitors. Although there are no specific recommendations, ARBs should not be used in patients with a history of ACE inhibitor-related angioedema, since angioedema is a potentially life-threatening condition. In addition, because of inhibition of aldosterone release by ARBs, hyperkalemia is a concern especially in those with renal insufficiency and, as with ACE inhibitors, progressive azotemia and renal failure might occur in those with bilateral renal artery stenosis or those with renal artery stenosis in a solitary kidney.

Recently, the first orally active renin inhibitor, aliskerin, became available. This agent blocks the renin–angiotensin system by inhibiting the rate-limiting step in angiotensin II (Ang II) biosynthesis. Unlike ACE inhibitors or ARBs which block either Ang II production or action and increase plasma renin activity, renin inhibitors suppress the generation of renin, but lead to elevation of the renin precursors, preprorenin and prorenin. Initially prorenin was thought to be biologically inactive, but the recent discovery of a renin receptor which can be activated by both renin and prorenin suggests that there may be separate pathways by which renin and prorenin can stimulate formation of Ang II.[37] Whether increased levels of prorenin may have a deleterious cardiovascular

effect in individuals with diabetes is unknown. Initial clinical studies indicate that aliskerin has a longer duration of action than ACE inhibitors or ARBs and has antihypertensive efficacy equal to that of ACE inhibitors and ARBs either as monotherapy or in combination with diuretics.[38,40] Outcome data from clinical trials in high-risk hypertensive patients, especially in those with diabetes, are pending.

JNC 7 recommended the use of ARBs as one of several alternative first-line therapies for patients with hypertension who cannot tolerate or do not respond to the recommended first-line medications. In addition, ARBs were also recommended as an initial therapy for those who could not tolerate ACE inhibitors (usually because of cough) and in whom ACE inhibitors are recommended as first-line drugs, such as patients with diabetes and proteinuria, heart failure, systolic dysfunction, post myocardial infarction, and those with mild renal insufficiency. However, data from randomized controlled trials in patients with type 2 diabetes suggest that ARBs may be considered equal to ACE inhibitors for renal protection.[41] Indeed, the reduction of endpoints in type 2 diabetes mellitus with the angiotensin losartan[42] (RENAAL), irbesartan in Diabetic Nephropathy Trial[43] (IDNT), and irbesartan in patients with type 2 Diabetes and Microalbuminuria Study Group[44] (IRMA trials) demonstrated that angiotensin II receptor blocker combined with conventional antihypertensive treatment as needed confers significant renal protection in patients with type 2 diabetes and nephropathy. In the RENAAL trial, the risk of the primary end point (a composite of doubling of serum creatinine, end-stage renal disease, or death from any cause) was reduced by 16% with losartan. In the same study, the risk of doubling of serum creatinine was reduced by 25% and the risk of end-stage renal disease was reduced by 28% over a follow-up period of 3.4 years. The study also documented reduction in the initial hospitalization for heart failure. These benefits were above and beyond those attributable to BP reduction alone.

Beta Blockers

BBs may be useful antihypertensive agents in the treatment of hypertension in patients with diabetes[2] when used as part of a multidrug regimen, but their value as monotherapy is less clear, according to JNC 7. In the UKPDS study, atenolol reduced microvascular complications of diabetes by 37%, strokes by 44%, and death related to diabetes by 32%. In that study, the efficacy of the BB and atenolol was equivalent to that of the ACE inhibitor, captopril, in reducing the micro- and macrovascular complications of diabetes, most probably secondary to their ability to modulate the RAAS system. In a nonrandomized study, hypertensive patients receiving BBs had a 28% higher risk of diabetes than untreated subjects. In contrast, patients with hypertension who received thiazide diuretics, ACE inhibitors, or CCBs were not found to be at increased risk for subsequent development of diabetes compared to patients receiving no medication.[3] However, increased risk for the development of diabetes with BB therapy was not found in other randomized studies.[45] Despite the possible adverse metabolic effects of BBs and their potential to mask symptoms of hypoglycemia, they have shown significant long-term favorable effects on CVD in hypertensive patients with diabetes and therefore, should be used in patients with diabetes, particularly those with coronary artery disease.

Calcium Channel Blockers

To achieve a target BP $\leq$130/80 mmHg, clinical trials suggest that at least 65% of patients require two or more antihypertensive agents. Additional therapies in people with diabetes (besides ACE inhibitors and diuretics) may include long-acting CCBs. A non-dihydropyridine CCB, such as verapamil or diltiazem, may have more beneficial effects on proteinuria than a dihydropyridine CCB, such as nifedipine. However, with the use of ACEs (or ARBs) with a diuretic as first-line treatment, the addition of a long-acting dihydropyridine such as amlodipine, nifedipine, or felodipine reduces both proteinuria and CVD event rates. If the targeted BP is still not achieved, a low-dose BB or an alpha/beta blocker can be added. It is important to note that both the ABCD[28] and AASK[46] trials demonstrated the superiority of ACEs over CCBs in prevention of CVD events; however, in the ABCD trial, the difference was likely the result of the beneficial effects of the ACE inhibitors rather than a negative effect of the CCB. The use of CCBs is particularly helpful in achieving the target BP, especially in patients with isolated systolic BP not responding to the addition of low-dose diuretic therapy.

Diuretics

Low-dose diuretics are effective antihypertensive agents in patients with diabetes as these patients often have expanded plasma volume. They may be used as monotherapy but are more often combined with ACE inhibitors, ARBs, BBs, or CCBs. Combination tablets may have advantages of cost, convenience, and patient adherence. In the ALLHAT diabetic subgroup, regimens containing the diuretic, chlothalidone, were as effective as ACE inhibitor- or CCB-based regimens in reducing fatal CHD and MI.[47] In contrast, the Second Australian National Blood Pressure trial reported a better prognosis in patients randomly assigned to an ACE-based treatment compared to a diuretic-based therapy.[48] The differences in outcomes may have reflected the ethnicity of the populations studied. Of concern in ALLHAT was the higher incidence of new-onset diabetes in the diuretic group, which over time could have substantial health consequences. Conversely, a report of 12,500 hypertensive adults did not find any influence of thiazide diuretics on the development of diabetes.[49] Hypokalemia has been observed with the use of large doses of hydrochlorothiazide (e.g., 50–200 mg) but is less likely in daily doses less than 25 mg.

Diuretics are also effective in the treatment of isolated systolic hypertension, which is common and occurs at a younger age in people with diabetes as discussed above. The systolic hypertension in the elderly program (SHEP) showed that small doses of chlorothalidone are not only safe but also effective, as evidenced by the reduced rate of major CVD events, fatal and nonfatal strokes, and all cause mortality in patients with diabetes.[2050] In addition, diuretics are often a necessary component of combination antihypertensive therapy in people with diabetes who often require three or more medications to achieve target BP.

Fixed-Dose Combination

The use of a fixed-dose combination therapy has the potential of enhancing compliance, reducing side effects, and cost of medications. Several diuretic-based combinations are available. These include those with beta blocker, ACE inhibitor, and ARB. These agents are being used increasingly. Our above-mentioned report indicates that 23% of patients with diabetes and hypertension are on a fixed-dose combination. Long-term benefits from these fixed-dose combinations remain to be seen. However, a combination of particular interest is that of a dihydropyridine CCB (amlodipine) and an ACE inhibitor (benazapril). Less pedal edema was reported with this combination than with CCB alone. This observation supports the notion that combination therapy might reduce side effects. In the above case, CCBs, being mainly arteriolar vasodilators, may induce pedal edema, but the addition of an ACE inhibitor with a balanced arterial and venous dilation reduces edema formation. This combination also showed enhanced rate of response compared to either placebo or each component given separately.

Summary

Rigorous treatment of hypertension, a common comorbid condition in patients with diabetes, is very important to reduce both microvascular and microvascular complications in this population. Combination therapy is often required to achieve and maintain blood pressure at the target level. The currently recommended target BP for patients with diabetes is 130/80 mmHg.

Based on the current evidence from randomized controlled trials, ACE inhibitors or ARBs are recommended as initial therapeutic agents with the addition of other agents as necessary to achieve and maintain target blood pressure.

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