Treatment of hypertension in the diabetic patient

Evidence demonstrates that a relationship exists between hypertension, Type 2 diabetes mellitus and several vascular and metabolic abnormalities that are components of the metabolic syndrome. Hypertension associated with the metabolic syndrome and Type 2 diabetes mellitus has pathophysiologic characteristics that provide clinical challenges as well as opportunities for successful therapeutic interventions. This article reviews the treatment of hypertension as a metabolic, as well as a vascular disease, and evaluates the paradigm for the treatment of the diabetic patient population with hypertension.

KEYWORDS: coronary heart disease ▪ diabetes ▪ hypertension ▪ metabolic syndrome ▪ treatment

Amgad N Makaryus[1†] & Samy I McFarlane[2]

[†]Author for correspondence:
[1]Department of Cardiology, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030, USA
Tel.: +1 516 562 1452
Fax: +1 516 562 1464
amakaryu@nshs.edu
[2]SUNY Downstate Medical Center, NY, USA

Type 2 diabetes mellitus is a common disease with substantial associated morbidity and mortality. One in every 14 Americans has diabetes, and another 40% of the population are at risk for developing the disease. Diabetes accounts for more than 200,000 deaths, 82,000 amputations, 44,400 new cases of end-stage renal disease and up to 24,000 new cases of blindness each year in the USA. A serious gap exists between established recommendations and the actual care that patients receive, especially with associated conditions such as hypertension, which further contribute to morbidity and mortality in these patients [1–3].

Most adverse diabetes outcomes are a result of vascular complications, both at a macrovascular level (coronary artery disease, cerebrovascular disease or peripheral vascular disease) and a microvascular level (retinopathy, nephropathy or neuropathy). The importance of preventing the macrovascular complications of Type 2 diabetes has started to receive greater attention. Numerous trials have examined the benefit of management of the highly prevalent risk factors, such as hypertension. Hypertension affects up to 60% of patients with Type 2 diabetes mellitus, and there are a growing number of pharmacologic treatment options [4–6]. The goals of this paper are to review the current literature based on recent trials and publications to evaluate the effects of management of hypertension on the complications of Type 2 diabetes, in order to provide an evidence base to guide clinicians in setting hypertension treatment goals and priorities in patients with Type 2 diabetes.

Pathogenesis of hypertension in Type 2 diabetes mellitus

Accumulating evidence indicates that both insulin resistance and the compensatory hyperinsulinemia may be causally related to hypertension. Hypertension is a major modifiable coronary heart disease (CHD) and chronic kidney disease (CKD) risk factor. The relationship between hypertension and risk of CHD events is continuous, consistent and independent of other risk factors. For individuals aged 40–70 years, each increment of 20 mmHg in systolic blood pressure (BP) or 10 mmHg in diastolic BP doubles the risk of CHD across the entire BP range from 115/75 to 185/115 mmHg [7]. Evidence from several randomized, controlled trials demonstrates that control of BP with antihypertensive therapy leads to mean reductions in stroke (35–40%), myocardial infarction (MI) (20–25%) and heart failure (50%) [8].

Insulin resistance contributes to the pathogenesis of hypertension through a number of abnormalities in insulin signaling and its associated cardiovascular and metabolic derangements [9]. These include resistance to effects of insulin on peripheral tissues and vasculature, as well as central actions of insulin leading to stimulation of the sympathoadrenal activity, activation of the renin–angiotension–aldosterone system (RAAS) and increased renal sodium reabsorption through suppressed atrial natriuretic peptide (ANP) activity. Other mechanisms that contribute to the etiology of hypertension in the insulin-resistant state include cell membrane ion exchange, endothelial dysfunction, left ventricular hypertrophy (LVH), cardiac hyperreactivity, dyslipidemia,

future medicine part of fsg

hyperglycemia, microalbuminuria, altered renal structure and function with impaired pressure natriuresis leading to sodium retention, volume expansion, progressive CKD and, eventually, end-stage renal disease. Microalbuminuria is recognized as not only a component of the cardiometabolic syndrome, but also as an early marker of renal impairment. Microalbuminuria is associated with the loss of normal nocturnal lowering of the systolic and diastolic BP, and reflects a state of generalized endothelial dysfunction. Microalbuminuria is therefore an important predictor of atherosclerosis, progressive renal disease and increased CHD morbidity and mortality [10].

Nonpharmacologic management options for hypertension in the diabetic patient population

In patients with diabetes, the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) [7] recommends a target BP of less than 130/80 mmHg in order to prevent death and disability associated with high BP. In patients with systolic pressures of 130–139 mmHg and diastolic pressures of 80–89 mmHg, lifestyle and behavioral therapy may be attempted for 3 months, although some believe the risk of hypertension in diabetes is so great that pharmacologic therapy should be instituted initially along with lifestyle modifications. Current guidelines consider a reduction in body weight by low caloric diet and physical exercise as the first and main treatment strategy in subjects with diabetes and the metabolic syndrome [11]. This requires changes in daily habits of the individual to achieve weight reduction and maintain body weight near ideal by appropriate dietary interventions and regular physical activity. Weight reduction is the single most important intervention that can improve hypertension control. Even a modest weight loss, up to 5–10% of initial body weight, may substantially reduce the risk of CHD. In the Diabetes Prevention Program, a lifestyle intervention including diet and regular exercise, achieving weight reduction of 5–7% of initial body weight, reduced the likelihood of diabetes by 58%, compared with 38% with metformin therapy. Adopting a healthy diet with reduction of salt and processed foods, saturated fats, trans-fatty acids, cholesterol and simple carbohydrates, moderation of alcohol intake, and increase in dietary fibers with the use of fruits and vegetables and adequate potassium intake, as outlined by the Dietary Approaches to Stop Hypertension (DASH) diet, lowers both BP and low-density lipoprotein (LDL) cholesterol. A realistic goal is to reduce body weight by 7–10% over 6–12 months through a relatively modest reduction of caloric intake (by 500–1000 calories/day). Both weight reduction and physical exercise improve glucose control, lipid levels and BP [12,13].

The effectiveness of intentional weight loss in reducing cardiovascular disease events in Type 2 diabetes was described in the Look-AHEAD trial. One-year changes in CHD risk factors were assessed in this multicenter, randomized, controlled trial of 5145 individuals with Type 2 diabetes, aged 45–74 years, with body mass index (BMIs) greater than 25 kg/m^2 (>27 kg/m^2 if taking insulin). An intensive lifestyle intervention involving group and individual meetings to achieve and maintain weight loss through decreased caloric intake and increased physical activity was compared with a diabetes support and education program. At 1 year, intensive lifestyle intervention resulted in clinically significant weight loss in people with Type 2 diabetes. This was associated with improved diabetes control and CHD risk factors and reduced medicine use in intensive lifestyle intervention versus the diabetes support and education program. Continued intervention and follow-up will determine whether these changes are maintained and will reduce CHD risk [14].

Pharmacologic management options for hypertension in the diabetic patient population

Despite the importance of nonpharmacologic lifestyle intervention measures, it is now recognized that pharmacologic therapy should often be instituted concomitantly. This strategy is based on a number of clinical trials that show the importance of drug therapy in reducing CHD in this high-risk group. In patients with diabetes, additional administration of antihypertensive, antidiabetic or lipid-lowering drugs is required when there is hypertension, diabetes or frank dyslipidemia, respectively. Since cardiovascular risk is high in hypertensive patients with diabetes, it is advisable to pursue rigorous BP control to lower BP to values less than the high normal ones that are common in diabetics. It is estimated that in patients with stage 1 hypertension (systolic BP between 140–159 mmHg and/or diastolic BP 90–99 mmHg) and additional CHD risk factors, achieving a sustained 12 mmHg decrease in systolic BP for 10 years will prevent one death for every 11 patients treated. In the presence of CHD or target-organ damage, only nine patients would require this BP reduction to prevent a death [15]. Evidence from the Hypertension

Optimal Treatment (HOT) trial demonstrated that patients with Type 2 diabetes mellitus may derive additional benefit from more intensive BP control to a target less than 80 mmHg diastolic BP [16]. Based on the association of moderately elevated BP with CHD and CKD risk, as well as the demonstrated benefits of further BP lowering, the JNC 7 recommends a BP goal of less than 130/80 mmHg in patients with diabetes [7].

A review of recently completed clinical trials indicates that greater than 65% of people with Type 2 diabetes mellitus and hypertension will require at least two different antihypertensive medications to achieve the suggested target BP of less than 130/80 mmHg [17,18]. Recommendations for these patients state that therapy in patients whose BP is more than 20/10 mmHg above target at diagnosis should be initiated with a combination of antihypertensive drugs, administered either as individual drugs or as fixed-dose combinations. Thiazide diuretics, β-blockers (BBs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) are beneficial in reducing CHD and stroke incidence in patients with Type 2 diabetes mellitus [17–19].

ACE inhibitors

ACE inhibitor therapy should be an integral component of any antihypertensive regimen in patients with Type 2 diabetes mellitus, as these agents have been demonstrated to reduce CHD [20,21] and CKD [22,23] in these populations. The ACE inhibitors and ARBs reduce the odds of developing new-onset Type 2 diabetes, and also decrease albuminuria. The ACE inhibitors provide cardioprotective and renoprotective benefits beyond their effect on BP. The use of the ACE inhibitor ramipril in the Heart Outcomes Prevention Evaluation (HOPE) trial, which included 9541 patients, 3577 of whom had Type 2 diabetes mellitus, was associated with a significant 25% risk reduction in MI, stroke or cardiovascular death after a median follow-up period of 4.5 years. This benefit was independent of any BP-lowering effect. Furthermore, the MICRO-HOPE substudy also showed that ramipril treatment was associated with a decreased risk of development of overt nephropathy in patients with Type 2 diabetes mellitus [22]. Another ACE inhibitor, captopril, also markedly lowered the risk for fatal and nonfatal MI, stroke and cardiovascular deaths than in the conventional therapy group in the Captopril Prevention Project [20].

Meta-analyses of ACE inhibitors have further supported this antiproteinuric effect to be independent of BP changes. In addition to the benefits of lowering the BP, ACE inhibitors also decrease intraglomerular pressure and glomerular membrane permeability to albumin, therefore contributing to decreases in microalbuminuria or overt proteinuria. ACE inhibitors have also been shown to slow the progression of nephropathy in microalbuminuric, normotensive patients compared with other antihypertensives [23].

Although ACE inhibitors are considered the medications of first choice, the issue of ACE inhibitor side-effect profile and tolerance needs to be considered. If a persistent cough secondary to the ACE inhibitor is intolerable and precludes its further use, then selection of an ARB is appropriate. Other complications of ACE inhibitor therapy, particularly in patients with diabetes, may be the progression of renal functional impairment and/or hyperkalemia. In these patients, a number of studies have supported the use of a CCB instead [24].

Angiotensin receptor blockers

The antihypertensive efficacy of ARBs is equivalent to ACE inhibitors, and they have been shown to have an improved side-effect profile over the ACE inhibitors. A comparison of irbesartan with enalapril in patients with severe hypertension demonstrated that irbesartan was associated with a significantly lower rate of coughing than with enalapril [25]. This may clinically translate to improved compliance with an ARB compared with an ACE inhibitor. Similar to ACE inhibitors, the use of ARB offers additional benefits in patients with Type 2 diabetes mellitus. The ARBs are renoprotective in addition to being cardioprotective.

The recent ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrated that the ARB telmisartan shows similar benefit to ramipril in high-risk vascular disease and diabetes patients. The ONTARGET trial enrolled 25,620 patients with CHD or diabetes plus additional risk factors who were over the age of 55 years but did not have evidence of heart failure. Patients were randomized to receive ramipril 10 mg per day, telmisartan 18 mg a day or a combination of the two. The mean duration of follow-up of the study was 55 months. Results showed that mean BP was lower in the telmisartan (a 0.9/0.6 mmHg greater reduction) and the combination-therapy group (a 2.4/1.4 mmHg greater reduction) than

in the ramipril group. At the end of the study, the primary end point (a composite of cardiovascular death, MI, stroke or hospitalization for heart failure) had occurred in a similar number of patients in all three groups. Compared with the ramipril group, telmisartan patients had lower rates of cough and angioedema and a higher rate of hypotensive symptoms, and patients given the combination treatment had higher rates of hypotensive symptoms, syncope, renal dysfunction and hyperkalemia, with a trend toward an increased risk of renal function requiring dialysis. This landmark trial demonstrates what researchers and clinicians have been assuming for a while – that ARBs are equivalent to ACE inhibitors with fewer side effects [26].

Another recent multicenter, prospective, two-armed, post-authorization study conducted over 9 months in 14,200 patients with uncontrolled hypertension with and without the metabolic syndrome found a significant improvement in BP and metabolic risk factors as a result of irbesartan treatment. There was no evidence of a difference between monotherapy and combination therapy with regard to the cardiovascular risk profile. Tolerability was excellent, with only 0.6% of patients experiencing an adverse event [27].

In the Losartan Intervention for Endpoint reduction (LIFE) trial, a subgroup of 1195 patients with diabetes, hypertension and signs of LVH on ECG were randomized to either a losartan-based or atenolol-based treatment. Mortality from all causes was 63 and 104 in losartan and atenolol groups, respectively (RR: 0.61 [0.45–0.84], p = 0.002), representing a significant 13% reduction in cardiovascular death, MI and a significant 25% reduction in the risk of stroke versus atenolol [27]. The subset of patients with Type 2 diabetes mellitus in this study had an even more significant reduction (24%) in the primary end point, as well as in cardiovascular mortality (37%) and total mortality (39%) when compared with atenolol. However, results of the Irbesartan in Diabetic Nephropathy Trial (IDNT), which compared irbesartan with a calcium antagonist, failed to show any significant difference between these two agents in terms of cardiovascular mortality [28]. However, both the IDNT and The Reduction of End points in NIDDM with Angiotensin II Antagonist Losartan (RENAAL) trials demonstrated that ARBs reduce proteinuria, the time to creatinine doubling and slow the progression of renal disease [29].

In the part of the published Action in Diabetes and Vascular Disease (ADVANCE) trial evaluating the lowering of BP, a reduction of 5.6 mmHg in the systolic BP among patients randomly assigned to receive perindopril and indapamide (a diuretic), as compared with those assigned to receive placebo, resulted in a relative risk reduction of 9% for the primary combined outcome. Thus, the expected relative risk reduction associated with a 1.6 mmHg reduction in systolic BP would be less than 3%. This suggests that the lower BP among patients undergoing intensive glucose control in this study probably explains some of the 10% reduction seen with intensive glucose control as compared with standard control. The explanation for the reduction in BP in the intensive-control group is unclear. The difference in BP so soon after randomization may indicate an early effect of the study treatment regimen; however, it is also possible that the difference reflects effects associated with more frequent contact with healthcare providers [30].

ACE inhibitors and ARBs have also been noted to exhibit BP-independent effects of RAAS blockade in patients with Type 2 diabetes mellitus. Multiple studies highlight these BP-independent effects of RAAS blockade, particularly in patients with Type 2 diabetes mellitus. These are the Captopril Prevention (CAPP) trial, HOPE [20,22] trial, MICRO-HOPE [22] substudy, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) trial [31] and Losartan Intervention For Endpoint reduction (LIFE) trial [32] among patients without Type 2 diabetes mellitus.

Diuretics

While thiazide diuretics have been shown to cause electrolyte imbalances, metabolic changes and volume contraction, thiazides have been the basis of antihypertensive therapy in most outcome trials. In these trials, including the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [18], diuretics have been very useful in preventing the CHD complications of hypertension. In ALLHAT, a subgroup of 12,063 patients (36%) with diabetes were randomized to treatment with chlorothalidone, amlodipine or lisinopril. There were no differences in the primary composite cardiovascular outcome between these three drugs, used in a very heterogeneous study population [18].

Diuretics enhance the antihypertensive efficacy of multidrug regimens. They are useful in achieving BP control and are more affordable than other antihypertensive agents. Thiazide diuretics, however, should be used cautiously in patients who have gout or who have a history

of significant hyponatremia. Additionally, some studies, including ALLHAT, have implicated thiazide diuretics in worsening of insulin resistance and increasing the risk of Type 2 diabetes mellitus [18].

β-blockers

As with thaizide diuretics, there is some evidence that BBs may increase the risk of new-onset Type 2 diabetes mellitus, and are therefore not recommended in subjects with the metabolic syndrome because of their adverse effect on the incidence of new-onset diabetes, as well as on body weight, insulin sensitivity and the lipid profile. However, these effects appear to be less pronounced or absent with the new vasodilating BBs, such as carvedilol and nebivolol, and these may therefore be considered in this patient population if target BP is not obtained with other medications. Furthermore, BBs are also of use in diabetes patients with concomitant evidence of coronary artery disease, such as anginal symptoms, including anginal equivalents or post-MI [33,34].

Calcium channel blockers

The nondihydropyridine CCBs, such as verapamil and diltiazem, have been shown to decrease proteinuria in diabetics. In combination therapy with ACE inhibitors, the nondihydropyridine CCBs have been shown to have additive effects in reducing albuminuria. The Syst-Eur trial using netrendipine demonstrated that intensive antihypertensive therapy for older patients with Type 2 diabetes and isolated systolic hypertension eliminated the additional risk for CHD events and stroke associated with diabetes [35]. In the HOT trial, there was a reduction in major CHD events with diastolic BP control in patients with diabetes when felodipine was used as first-line therapy [16].

Other classes of drugs

Many new classes of agents that may be useful in the treatment of this patient population have been developed and continue to be tested and examined. Among these agents, two of the most notable are the anti-aldosterone drugs and α-1-antagonists. It is felt that in the setting of long-term ACE-inhibitor or ARB therapy, aldosterone receptor antagonists (spironolactone and eplerenone) provide another rational therapeutic approach for patients whose BP is not controlled by the standard therapies [36]. A recent study evaluated the use of the antialdosterone spironolactone and the α-1-antagonist doxazosin as treatment for patients with resistant hypertension. This study involved 181 outpatients with resistant hypertension (defined as a failure of BP control despite treatment with three drugs, one of which was a diuretic) who received additional spironolactone (n = 88) or doxazosin (n = 93). Mean systolic BP in the spironolactone group dropped by 28 mmHg (95% CI: 24–32 mmHg; $p < 0.001$) and mean diastolic BP dropped by 12 mmHg (95% CI: 9–14 mmHg; $p < 0.001$). The corresponding decreases in the doxazosin group were 16 mmHg (95% CI: 13–20 mmHg; $p < 0.001$) and 7 mmHg (95% CI: 5–9 mmHg; $p < 0.001$), respectively. The decrease was significantly greater with spironolactone for both systolic ($p < 0.001$) and diastolic ($p = 0.003$) pressures. At the end of follow-up, 30% of all patients had achieved BP control, with control being more frequent with spironolactone (39%) than doxazosin (23%; $p = 0.02$). Multivariate logistic regression analysis demonstrated that the only factors that significantly influenced the achievement of BP control were diabetes (odds ratio: 0.17; 95% CI: 0.08–0.39; $p < 0.001$) and baseline systolic BP less than 165 mmHg (odds ratio: 2.56; 95% CI: 1.11–5.90; $p = 0.03$). The study concludes that in patients with resistant hypertension, the addition of either spironolactone or doxazosin resulted in a significant decrease in BP, although the decrease appeared to be greater with spironolactone. The presence of diabetes in this study was found to complicate adequate BP control [37].

Future perspective & current unanswered areas in treatment & management

Therapy aimed at improving insulin sensitivity and RAAS blockade seems to offer survival benefits to diabetics with hypertension. Further research in identifying the mechanism of hypertension, diabetes and insulin resistance can shed more light on the elusive link that connects these seemingly different disease processes. General consensus holds that intense lifestyle measures should remain the main treatment approach in diabetics with hypertension, but that in some cases, consideration might be given to drugs such as blockers of the renin–angiotensin system for their potential ability to prevent new-onset hypertension and new-onset diabetes, and some of the organ damage that is particularly common in this high-risk condition of hypertension in the setting of diabetes [8]. The recently published Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study examined the addition of aliskiren, an oral direct renin inhibitor, to treatment in 599 patients with the maximal

recommended dose of losartan (100 mg daily) and optimal antihypertensive therapy in patients who had hypertension and Type 2 diabetes with nephropathy. Aliskiren was found to possibly have renoprotective effects that are independent of its blood-pressure-lowering effect in patients with hypertension, Type 2 diabetes and nephropathy who are receiving the recommended renoprotective treatment [38].

One of the limitations of the current literature is a lack of strong evidence comparing the effects of BP treatment according to demographic factors, such as ethnicity and age. These factors are important because ethnicity may be a strong predictor of adverse events in patients with diabetes, and age may change relative or absolute benefits of hypertension treatment, in part because of competing risks for death. In addition, the effectiveness of different antihypertensive agents in BP lowering may vary by ethnicity and age. For example, in ALLHAT, African–American participants did not respond to ACE inhibitors as well as other participants, and had a higher risk for stroke as a result. However, it is not clear how these results relate to the population of African–American persons with diabetes. Further studies in diabetic subpopulations are necessary with respect to ideal management of hypertension [18].

Evidence is also inconclusive as to whether, in the absence of diabetes, patients with the metabolic syndrome may benefit from the use of antidiabetic drugs. A recent review of five prospective trials using α-glucosidase inhibitors in individuals with impaired fasting glucose showed a decreased incidence of Type 2 diabetes. No significant difference was found in mortality, other types of morbidity, glycated hemoglobin and BP [8,39]. The insulin sensitizers thiazolidinediones have received approval to be used for the treatment of Type 2 diabetes because of their ability to stimulate the peroxisome proliferator-activated receptor-γ (PPR-γ). One of these compounds (rosiglitazone) has been tested in patients with impaired glucose tolerance and has been shown to be significantly effective in preventing new-onset diabetes [40]. However, although rosiglitazone has been shown to reduce progression to Type 2 diabetes, its use for this purpose is not recommended in current guidelines, and is not used clinically for this purpose. Furthermore, there has been controversy associated with increased ischemic cardiovascular events with rosilgitazone, and this was addressed in the recent American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus on management of hyperglycemia [41].

Long-term reductions in body weight and waist circumference, as well as favorable changes in other metabolic risk factors for cardiovascular disease, such as plasma glucose, HDL cholesterol, serum triglycerides and insulin resistance, have recently been reported with the use of the endocannabinoid C1 receptor blocker rimonabant in placebo-controlled studies [8,40]. There is also some evidence that administration of the drug does not increase, and may even cause some BP reduction, and its impact is currently being further assessed in a prospective fashion. A recent trial, the STRADIVARIUS study [42], showed disappointing results with failure of rimonabant to reduce atherosclerotic plaque volume despite improvement in central obesity, dyslipidemia and weight reduction, suggesting that improvement in CHD surrogate markers does not necessarily translate to overt CHD benefit. Despite these possible metabolic effects, a major problem with depression/suicidal ideation has been noted with rimonabant, and the US FDA has ruled not to approve this drug for use in the USA [40,43,44].

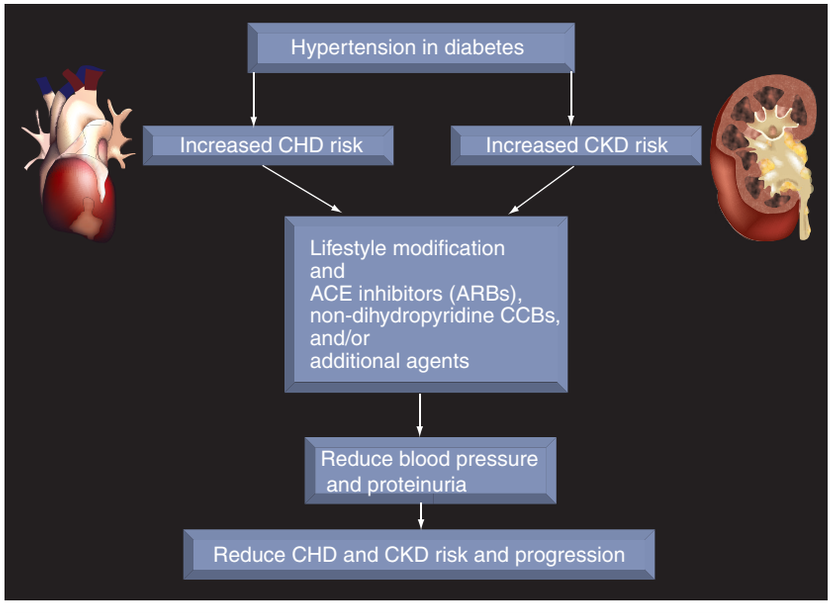

Figure 1. Treatment of hypertension in diabetes. ARB: Angiotensin-receptor blocker; CCB: Calcium channel blocker; CHD: Coronary heart disease; CKD: Chronic kidney disease.

Conclusion

The close relationship between diabetes and hypertension suggests a possible common genetic or pathophysiological process underlying their connection. Hypertension and diabetes are associated with an increased risk of CHD and CKD. It is imperative that hypertension

Executive summary

Pathogenesis of hypertension in Type 2 diabetes mellitus

- Type 2 diabetes mellitus is a common disease, with substantial associated morbidity and mortality.
- Hypertension affects up to 60% of patients with Type 2 diabetes mellitus, and there are a growing number of pharmacologic treatment options.
- Accumulating evidence indicates that both insulin resistance and the compensatory hyperinsulinemia may be causally related to hypertension.
- Insulin resistance contributes to the pathogenesis of hypertension through a number of abnormalities in insulin signaling and its associated cardiovascular and metabolic derangements.

Nonpharmacologic management options for hypertension in the diabetic patient population

- In patients with diabetes, the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends a target blood pressure of less than 130/80 mmHg in order to prevent death and disability associated with high blood pressure.
- In patients with systolic pressures of 130–139 mmHg and diastolic pressures of 80–89 mmHg, lifestyle and behavioral therapy may be attempted for 3 months, although some believe the risk of hypertension in diabetes is so great that pharmacologic therapy should be instituted initially along with lifestyle modifications.

Pharmacologic management options for hypertension in the diabetic patient population

- Despite the importance of nonpharmacologic lifestyle intervention measures, it is now recognized that pharmacologic therapy should often be instituted concomitantly.
- In patients with diabetes, additional administration of antihypertensive, antidiabetic or lipid-lowering drugs is required when there is hypertension, diabetes or frank dyslipidemia, respectively.
- Recently completed clinical trials indicate that greater than 65% of people with Type 2 diabetes mellitus and hypertension will require at least two different antihypertensive medications to achieve the suggested target blood pressure of less than 130/80 mmHg.
- Angiotensin converting enzyme (ACE) inhibitor therapy should be an integral component of any antihypertensive regimen in patients with Type 2 diabetes mellitus, as these agents have been demonstrated to reduce coronary heart disease (CHD) and chronic kidney disease (CKD) in these populations.
- The antihypertensive efficacy of angiotensin receptor blockers (ARBs) is equivalent to ACE inhibitors, and they have been shown to have an improved side effect profile over the ACE inhibitors.
- While thiazide diuretics have been shown to cause electrolyte imbalances, metabolic changes and volume contraction, thiazides have been the basis of antihypertensive therapy in most outcome trials.
- There is some evidence that β-blockers may increase the risk of new-onset Type 2 diabetes mellitus, and are therefore not recommended in subjects with the metabolic syndrome because of their adverse effect on the incidence of new-onset diabetes, as well as on body weight, insulin sensitivity and the lipid profile. These effects, however, appear to be less pronounced or absent with the new vasodilating β-blockers, such as carvedilol and nebivolol, and these may therefore be considered in this patient population if target blood pressure is not obtained with other medications.
- The nondihydropyridine calcium channel blockers, such as verapamil and diltiazem, have been shown to decrease proteinuria in diabetics. In combination therapy with ACE inhibitors, the nondihydropyridine calcium channel blockers, have been shown to have additive effects in reducing albuminuria.
- It is felt that in the setting of long-term ACE inhibitor or ARB therapy, aldosterone receptor antagonists (spironolactone and eplerenone) and/or α-1-antagonists provide another rational therapeutic approach for patients whose blood pressure is not controlled by the standard therapies.

Future perspective & current unanswered areas in treatment & management

- Therapy aimed at improving insulin sensitivity and renin–angiotensin–aldosterone system blockade seems to offer survival benefits to diabetics with hypertension.
- Further research in identifying the mechanism of hypertension, diabetes and insulin resistance can shed more light on the elusive link that connects these seemingly different disease processes.
- General consensus holds that intense lifestyle measures should remain the main treatment approach in diabetics with hypertension, but that in some cases, consideration might be given to drugs such as blockers of the renin–angiotensin–aldosterone system for their potential ability to prevent new-onset hypertension and new-onset diabetes; and some of the organ damage that is particularly common in this high-risk condition of hypertension in the setting of diabetes.

Conclusion

- The close relationship between diabetes and hypertension suggests a possible common genetic or pathophysiological process underlying their connection.
- Hypertension and diabetes are associated with increased risk of CHD and CKD. It is imperative that hypertension is controlled rigorously to prevent or decrease the risk of CHD and CKD.
- Therapeutic lifestyle changes with weight reduction, increased physical activity and healthy diet are first-line therapies for these patients.
- Hypertension should be treated aggressively following JNC 7 recommendations. ACE inhibitors or ARBs are generally considered the treatment of choice for hypertension in diabetic patients, especially when concomitant CKD is present.
- Targeting the individual risk factors such as hypertension, obesity and dyslipidemia has been shown to reduce the CHD events in multiple studies and affect outcomes in these diabetic patients.

is controlled rigorously to prevent or decrease the risk of CHD and CKD. The treatment of hypertension in diabetes, as Figure 1 depicts, is complex, and encompasses many interactive regulatory systems. Therapeutic lifestyle changes with weight reduction, increased physical activity and healthy diet are first-line therapies for these patients. Hypertension should be treated aggressively following JNC 7 recommendations. ACE inhibitors or ARBs are generally considered the treatment of choice for hypertension in diabetic patients, especially when concomitant CKD is present. Targeting the individual risk factors such as hypertension, obesity and dyslipidemia has been shown to reduce the CHD events in multiple studies, and affect outcomes in these diabetic patients.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:
- ▪ of interest
- ▪▪ of considerable interest

1 Lloyd-Jones D, Adams R, Carnethon M *et al.*: Heart Disease and Stroke Statistics – 2009 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 119, 80–486 (2009).

▪▪ **This is the most recent update to the heart disease statistics kept by the American Heart Association. It contains helpful information that puts this discussion into perspective.**

2 Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27(5), 1047–1053 (2004).

3 Pinhas-Hamiel O, Zeitler P: The global spread of Type 2 diabetes mellitus in children and adolescents. *J. Pediatr.* 146(5), 693–700 (2005).

4 Suzuki T, Homma S: Treatment of hypertension and other cardiovascular risk factors in patients with metabolic syndrome. *Med. Clin. North Am.* 91(6), 1211–1223 (2007).

5 Harris MI, Flegal KM, Cowie CC *et al.*: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988–1994. *Diabetes Care* 21, 518–524 (1998).

6 Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. *Diabet. Med.* 15, 539–553 (1998).

7 Chobanian AV, Bakris GL, Black HR *et al.*: National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 289(19), 2560 –2571 (2003).

▪▪ **This is an important guideline statement that underlies many of the treatment algorithms for hypertension.**

8 Mancia G, De Backer G, Dominiczak A *et al.*:; the task force for the management of arterial hypertension of the European Society of Hypertension; the task force for the management of arterial hypertension of the European Society of Cardiology: 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur. Heart J.* 28(12), 1462–1536 (2007).

▪▪ **This is an excellent up-to-date guideline statement on the management of hypertension from the European Society of Cardiology.**

9 Malik S, Wong ND, Franklin SS *et al.*: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 110, 1245–1250 (2004).

10 Natali A, Pucci G, Boldrini B, Schillaci G: Metabolic syndrome: at the crossroads of cardiorenal risk. *J. Nephrol.* 22(1), 29–38 (2009).

11 Mancia G, Bousquet P, Elghozi JL *et al.*: The sympathetic nervous system and the metabolic syndrome. *J. Hypertens.* 25(5), 909–920 (2007).

12 Whaley-Connell A, Palmer J, Sowers JR: Risk stratification and treatment options for hypertensive patients with metabolic syndrome and prediabetes. *Johns Hopkins Advanced Studies Med.* 5(10C), S1011–S1018 (2005).

13 Sacks FM, Svetkey LP, Vollmer WM *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.* 344, 3–10 (2001).

14 Look AHEAD Research Group; Pi-Sunyer X, Blackburn G, Brancati FL *et al.*: Reduction in weight and cardiovascular disease risk factors in individuals with Type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 30(6), 1374–1383 (2007).

15 El-Atat F, Aneja A, Mcfarlane S, Sowers J: Obesity and hypertension. *Endocrinol. Metab. Clin. North Am.* 32, 823–854 (2003).

16 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* 351, 1755–1762 (1998).

17 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* 265, 3255–3264 (1991).

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. *JAMA* 288, 2981–2997 (2002).

▪ **This is a landmark trial that assessed the efficacy of the various antihypertensive medications.**

19 Israili ZH, Lyoussi B, Hernández-Hernández R, Velasco M: Metabolic syndrome: treatment of hypertensive patients. *Am. J. Ther.* 14(4), 386–402 (2007).

20 Hansson L, Lindholm LH, Niskanen L *et al.*: Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. *Lancet* 353, 611–616 (1999).

21 Yusuf S, Sleight P, Pogue Bosch J, Davies JR, Dagenais G: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N. Engl. J. Med.* 342, 145–153 (2000).

22 Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 355, 253–259 (2000).

23 Khan K, Govindarajan G, Whaley-Connell A, Sowers JR: Diabetic hypertension. *Heart Fail. Clin.* 2, 25–36 (2006).

24 Sowers JR, Reed J: Clinical advisory treatment of hypertension in diabetes. *J. Clin. Hypertens.* 2(2),132–133 (2002).

25 Larochelle P, Clack JM, Marbury TC, Sareli P, Kreiger EM, Reeves RA: Effects and tolerability of irbesartan versus enalapril in patients with severe hypertension. *Am. J. Cardiol.* 80, 1613–1615 (1997).

26 Yusuf S, Teo KK, Pogue J *et al.* for the ONTARGET investigators: telmisartan, ramipril, or both in patients at high risk for vascular events. *N. Engl. J. Med.* 358, 1547–1559 (2008).

▪ **This recent landmark trial demonstrates what researchers and clinicians have been assuming for a while, that angiotensin receptor blockers are equivalent to angiotensin converting enzyme inhibitors, with fewer side effects.**

27 Kintscher U, Bramlage P, Paar WD, Thoenes M, Unger T: Irbesartan for the treatment of hypertension in patients with the metabolic syndrome: a sub analysis of the Treat to Target post authorization survey. Prospective observational, two armed study in 14,200 patients. *Cardiovasc. Diabetol.* 6, 12 (2007).

28 Lewis EJ, Hunsicker LG, Clarke WR *et al.*: Renoprotective effect of the angiotensin-receptor antagonist irbersartan in patients with nephropathy due to Type 2 diabetesand nephropathy. *N. Engl. J. Med.* 345, 861–869 (2001).

29 Whaley-Connell A, Sowers JR: Hypertension management in Type 2 diabetes and the JNC VII. In: *Endocrinology and Metabolism Clinics of North Amercia.* Einhorn D, Rosenstock J (Eds.). WB Saunders Company, Philadelphia, PA, USA, 34(1), 63–75 (2005).

30 Patel A, MacMahon S, Chalmers J *et al.*: Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with Type 2 diabetesmellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 370(9590), 829–840 (2007).

31 Pfeffer MA, Swedberg K, Granger CB *et al.*: Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 362(9386), 759–766 (2003).

32 Lindholm LH, Ibsen H, Dahlof B *et al.*: Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For End point reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359, 1004–1010 (2002).

33 Palaniappan L, Carnethon MR, Wang Y *et al.*: Insulin Resistance Atherosclerosis Study. Predictors of the incident metabolic syndrome in adults: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 27(3), 788–793 (2004).

34 Kaiser T, Heise T, Nosek L, Eckers U, Sawicki PT: Influence of nebivolol and enalapril on metabolic parameters and arterial stiffness in hypertensive type 2 diabetic patients. *J. Hypertens.* 24, 1397–1403 (2006).

35 Birkenhager WH, Staessen JA, Gasowski J, de Leeuw PW: Effects of antihypertensive treatment on endpoints in the diabetic patients randomized in the Systolic Hypertension in Europe (Syst-Eur) trial. *J. Nephrol.* 13(3), 232–237 (2000).

36 Basile J: New therapeutic options in patients prone to hypertension: a focus on direct renin inhibition and aldosterone blockade. *Am. J. Med. Sci.* 337(6), 438–444 (2009).

37 Rodilla E, Costa JA, Pérez-Lahiguera F, Baldó E, González C, Pascual JM: Spironolactone and doxazosin treatment in patients with resistant hypertension. *Rev. Esp. Cardiol.* 62(2), 158–166 (2009).

38 Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators: Aliskiren combined with losartan in Type 2 diabetesand nephropathy. *N. Engl. J. Med.* J358(23), 2433–2446 (2008).

39 Van de Laar FA, Lucassen PL, Akkermans RP *et al.*: α-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose. *Cochrane Database Syst. Rev.* 4, CD005061 (2006).

40 Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J: RIO-North America Study Group: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 295, 761–775 (2006).

41 Nathan DM, Buse JB, Davidson MB *et al.*; American Diabetes Association; European Association for the Study of Diabetes: Medical management of hyperglycaemia in Type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 52(1), 17–30 (2009).

▪▪ **This is an important algorithm statement that highlights many of the treatment algorithms for Type 2 diabetes mellitus.**

42 Nissen SE, Nicholls SJ, Wolski K *et al.*; STRADIVARIUS Investigators: Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *JAMA* 299(13), 1547–1560 (2008).

43 Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF; RIO-Diabetes Study Group: Efficacy and tolerability of rimonabant in overweight or obese patients with Type 2 diabetes. *Lancet* 368, 1160–1172 (2006).

44 Cahill K, Ussher M: Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation. *Cochrane Database Syst. Rev.* 4, CD005353 (2007).