## Review Article

# Treatment Dilemmas in Hypertension Management in Diabetes

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## ABSTRACT

Hypertension is a common comorbidity in diabetes. It is important in pathogenesis of its macrovascular and microvascular complications and concomitant hypertension increase the risk of polyvascular complications of diabetes. In diabetic hypertensives, an early diagnosis, treatment optimization, prevention of therapy and disease-related complications, and minimising drug interactions are common important dilemmas in hypertension management. Both pharmacological and non-pharmacological means must be used for management of blood pressure (BP). For drug therapy, angiotensin receptor blockers are the first line drug and dihydropyridine calcium channel blockers are the first add-on drug in majority of cases. With the recent advent of antidiabetic drugs, such as SGLT2-inhibitors and GLP-1 receptor agonists that influence BP, a new dimension in hypertension management has emerged. It is important to not only control BP but also manage other vascular risk factors, incorporating patient's needs and ensuring long term compliance. This individualization of therapy is the need of the hour.

**Keywords:** High blood pressure, Novel anti-diabetic drugs, Pharmacotherapy, Type 2 diabetes.

## INTRODUCTION

Hypertension is the most common associated morbidity in diabetes patients, with the prevalence depending on type and duration of disease, age, race and ethnicity of patient, body mass index (BMI), and presence of associated kidney disease.[1] The prevalence of hypertension among diabetic people is twice as common as compared to general population.[2] Moreover, the presence of hypertension does increase the risk of new-onset diabetes, as well as diabetes does promote development of hypertension. Whatever the case, hypertension is at the same time, a common strong risk factor for associated micro and macro vascular complications of diabetes, namely acute coronary syndrome, angina, myocardial infarction, stroke, peripheral vascular disease, retinopathy, and nephropathy.[3] Therefore, when left untreated or poorly controlled, hypertension can significantly accelerate the development and progression of both the micro and macrovascular complications of diabetes and on the other hand well controlled BP significantly reduces the incidence of complications irrespective of effect of glycemic control, making hypertension a well proven associated as well as independent risk factor for complications among diabetics. Thus, there is need of proper management of BP in already high risk patients such as diabetics.[3]

The ideal treatment of hypertension among diabetics further carries its own challenges and dilemmas, ranging from drug to drug interactions, precipitating disease related complications, e.g. increased incidence of orthostatic hypertension among patients with diabetic autonomic neuropathy taking calcium channel blockers (CCBs), interaction of drug with complication precipitated by disease per se, e.g. potassium imbalance in patients with diabetic nephropathy taking angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARBs), risk of excessive lowering of BP in those with cardiovascular diseases and the adverse effects, etc. Hence an individualized approach for BP management in diabetes is needed. This article is intended to update these dilemmas in treatment of hypertension among people with diabetes.

## BP MEASUREMENT PROTOCOL IN DIABETES

BP should be measured at every routine clinical visit. At the initial visit, it is must to measure BP in both arms to detect and account for abnormalities that may lead to spurious readings, such as arterial stenosis. Patients with elevated

BP (≥140/90 mmHg) who are not known to have hypertension should have elevated BP confirmed on subsequent visits usually within a month or should undergo home BP measurement to confirm the diagnosis of hypertension. Orthostatic measurement of BP should be performed during initial evaluation of hypertension and periodically at follow-up, or when symptoms of orthostatic hypotension are present, and regularly if orthostatic hypotension has been diagnosed. Special note must be made of patients with white coat or masked hypertension which is commonly present in patients with autonomic dysfunction that is more common in diabetic patients.

## PATHOPHYSIOLOGY

Patients of hypertension and diabetes or metabolic syndrome show slow-grade inflammation occurring at the vasculature level resulting in vascular remodelling, endothelial dysfunction, and vascular stiffness predisposing to development and progression of cardiovascular diseases.[4] Patients with metabolic syndrome show increased expression and plasma concentration of different inflammatory markers and mediators, including C-reactive protein (CRP) and several adhesion molecules (selections, ICAM-1, VCAM-1).[5] In particular, high levels of inflammatory mediators, particularly IL-6, ICAM-1, and CRP have been demonstrated in patients with hypertension and also have been associated with the risk for developing hypertension among normotensive patients.[6] Also, abnormal activation of the renin-angiotensin system (RAS) may play a central role in the pathophysiology and development of cardiovascular disease in these settings. In particular, angiotensin II induces vascular remodelling and injury by several mechanisms including vasoconstriction, cell growth, oxidative stress, and inflammation.[7] These molecules induce and maintain inflammation within the vascular wall, stimulate deposition of extracellular matrix, and promote hypertrophy and/or hyperplasia of vascular smooth muscle cells. A large body of evidence underlines the pathophysiological role played by inflammation in the progression of cardiovascular and metabolic disease and in the triggering of cardiovascular events, as well as the need to oppose pharmacologically these mechanisms to improve cardiovascular outcomes, as shown in figure 1. Second known pathophysiological mechanism for development of hypertension among diabetics is increased extra cellular fluid (ECF) due to hyperglycemia and increased renin-angrotension aldosterone system (RAAS )activity.

## HYPERTENSION MANAGEMENT

The factor unique to blood pressure control which needs special mention is lack of legacy effect[8] which was reported with the long-term emergent and/or sustained benefits of early improved glycemic control with the UK Prospective Diabetes Study (UKPDS) report. Similar results were obtained by the Hypertension in Diabetes Study (HDS) carried out in the frame of UKPDS, with no evidence of

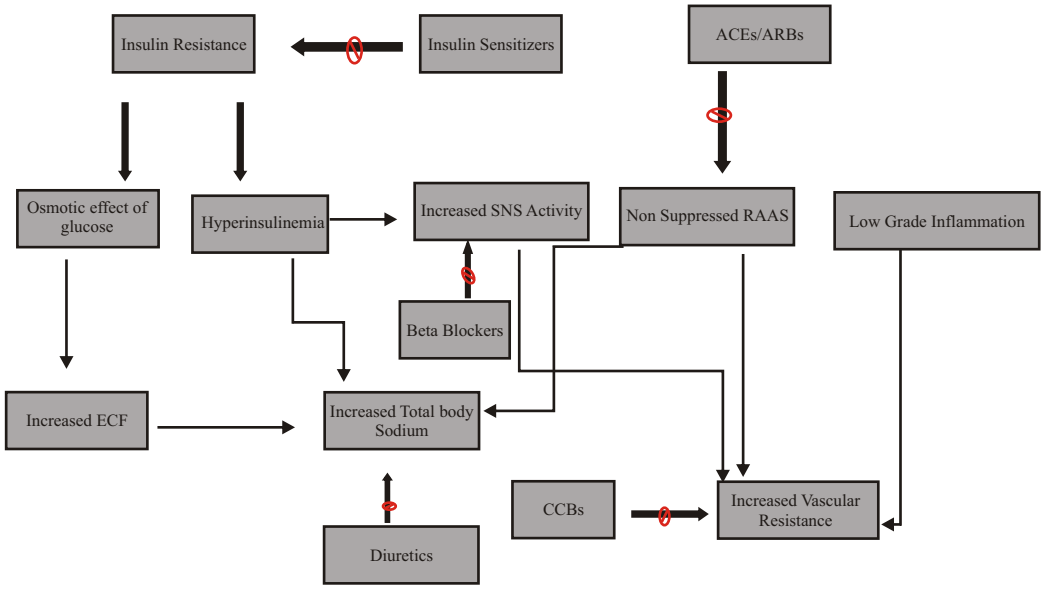


**Figure 1: Pathophysiology of raised blood pressure in diabetes.**

any legacy effect on cardiovascular (CV) outcomes for an initial 4 year period of tight blood pressure (BP) control. Thus, it was concluded that BP control has to be continued over time. Another factor which needs a special mention is early start of therapy; data in favour of long-term benefits of an early start of antihypertensive treatment come from the Syst-Eur study. After 4 years of follow-up (6 years, counting from randomization), patients who received early antihypertensive treatment, as compared with patients who initially received placebo, had a significantly greater reduction in the risk of stroke (28%), CV complications (15%), and total mortality (13%). Hence hypertension is meant not only to be managed effectively in diabetic patients; treatment should begin at early stages and must be continued.

Treatment of hypertension to blood pressure <140/90 mmHg is supported by unequivocal evidence that pharmacologic treatment of blood pressure ≥140/90 mmHg reduces cardiovascular events as well as some microvascular complications. In type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) showed that targeting blood pressure <150/85 mmHg versus <180/105 mmHg reduced composite microvascular and macrovascular diabetes complications by 24%.[8] Moreover, meta-analyses of clinical trials demonstrate that antihypertensive treatment of populations with diabetes and baseline blood pressure ≥140/90 mmHg reduces the risks of ASCVD, heart failure, retinopathy, and albuminuria. Therefore, most patients with type 1 or type 2 diabetes who have hypertension should, at a minimum, be treated to blood pressure targets of <140/90 mmHg. Intensification of antihypertensive therapy to target blood pressures lower than <140/90 mmHg (e.g. <130/80 or <120/80 mmHg) may be beneficial for selected patients with diabetes.

Interventions to prevent hypertension include both pharma cological (Table 1) and non-pharmacological methods. Non-pharmacologic methods include dietary salt restriction, weight reduction, Dietary Approaches to Stop hypertension (DASH) diet, exercise, alcohol restriction. This is consistent with the American Diabetes Association (ADA) 2017 guidelines, which state that among patients with a systolic blood pressure ≥120 mmHg or a diastolic pressure ≥80, such non-pharmacologic methods should be used to reduce blood pressure. Pharmacologic agents should be initiated in patients, whose blood pressure is ≥140/≥90 mmHg or ≥130/≥80 mmHg, depending upon risk for cardiovascular disease. Body weight reduction and aerobic exercise increases insulin sensitivity and improves both blood glucose and blood pressure control. Weight loss in overweight or obese individuals can lead to a significant fall in blood pressure independent of exercise. The decline in blood pressure induced by weight loss can also occur in the absence of dietary sodium restriction, but even modest sodium restriction may produce an additive antihypertensive effect. The weight loss-induced decline in blood pressure generally ranges from 0.5 to 2 mmHg for every 1 kg of weight lost. On the other hand in people with diabetes who had an intentional weight loss, a reduction in total mortality and a reduction in cardiovascular disease-plus-diabetes mortality is seen. Among diabetics, "memory" effect of intentional weight loss is also seen, which may be sustained for a long duration even if the weight loss is not fully maintained. Similar to the effect of timing on control of hypertension on Diabetes Mellilus (DM) patients, weight loss also plays an important role in the course of the disease process, when insulin resistance is still prominent phenomenon; either energy restriction or weight loss will improve blood glucose levels. But as the disease progresses and insulin deficiency becomes more prominent, it may be too late for weight loss to be helpful. In fact, at later stages of the disease, when medications, including insulin, need to be combined with nutrition therapy, prevention of weight gain often becomes the goal. DASH diet approach promotes consumption of a variety of foods (whole grains, fat-free or low-fat dairy products, fruits, vegetables, poultry, fish, and nuts). DASH eating plan, in view of its impact on improvement of insulin resistance, is an acceptable eating pattern for people who have diabetes, in addition to patients with high BP.

All antihypertensive drugs lower BP, and their main benefit, based on a large number of randomized trials, is due to lowering of BP per se and is largely independent of the drugs employed. However, differences between drugs exist with respect to target-organ damage and prevention of cardiovascular events. Therefore, treatment should be individualized according to concomitant risk factors and diseases and depend on age, biochemical, and hemodynamic measurements of the patients. In the guidelines from ESH/European Society of Cardiology,

**Table 1: Drug classes for hypertension management in diabetes**

| Drug class | Sub-types | Common examples (India) *Alphabetic order* |
|---|---|---|
| **Renin angiotensin aldosterone system (RAAS) blockers** | Angiotensin converting enzyme (ACE) inhibitors | Captopril, Lisinoprol, Perindopril, Ramipril, |
| | Angiotensin receptor blockers (ARBs) | Azilsartan, Irbesartan, Losartan, Olmesartan, Telmisartan |
| | Aldosterone antagonists | Spirolactone |
| **Calcium channel blockers (CCB)** | Dihydropyridine | Amlodipine, Cilnidipine, Nifedipine |
| | Non-dihydropyridine | Diltiazem, Verapamil |
| **Diuretics** | Thiazides | Hydrochlorothiazide |
| | Thiazide like loop diuretics | Chlorthalidone, Indapamide, |
| **Beta blockers** | | Atenolol, Bisoprolol, Carvedilol, Metoprolol, |
| **Alpha blockers** | | Doxazosin, Prazosin |

thiazide diuretics, β-blockers, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) are recommended as suitable for initiation and maintenance of antihypertensive treatment either as monotherapy or in suitable combinations. Most patients require multiple drugs (often three to four different drugs) to achieve BP targets and unfortunately, many patients still remain untreated or undertreated, particularly among women and minority populations. In the USA, it has been calculated that only 30% of the diabetic population reach the BP target[9](<130/80 mmHg).

## Renin-angiotensin-aldosterone system (RAAS) blockers

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have long been considered the cornerstone of anti-hypertensive treatment in diabetic patients. Previous studies have demonstrated that both renin-angiotensin-aldosterone system (RAAS) blockers, ACEIs and ARBs, are associated with prevention of new onset DM in hypertensive patients and are particularly favourable among patients with albuminuria. ACEIs were reported to reduce overall CV risk, overt nephropathy, renal failure, and retinopathy among non-hypertensive diabetics. The ONTARGET study, comparing ACEIs and ARBs in preventing all-cause mortality and CV morbidity and mortality, outcome was similar between the two drug classes and although ARBs were found to be more effective than ACEIs in the prevention of stroke in few studies. Therefore, it seems that ACEIs and ARBs are probably equally efficacious for the prevention of CV outcomes in hypertensive diabetics. ARBs and ACEIs are equally effective in preventing progression of kidney disease in diabetic patients with early nephropathy with ARBs having comparable BP lowering capacity with fewer side effects compared with ACEIs. Combining two RAAS blockers is discouraged based on the discouraging results of the Aliskiren Trial in Type 2 Diabetes Using Cardio-renal Endpoints (ALTITUDE) and the ONTARGET trials. A recent meta-analysis of 19 randomized controlled trials with over 25,000 participants found that ACEIs or ARBs were associated with a similar risk of death (relative risk 0.99, 95% CI 0.931.05), CV death (1.02, 0.831.24), myocardial infarction (0.87, 0.641.18), angina pectoris (0.80, 0.581.11), stroke (1.04, 0.921.17), heart failure (0.90, 0.761.07), revascularization (0.97, 0.771.22), and end stage renal disease (0.99, 0.781.28) as compared with other anti-hypertensive agents.[10] In summary, it seems that use of ACEIs or ARBs is not superior to use of other anti-hypertensive agents in diabetics without evidence of nephropathy, but these classes are legitimate first-line treatment options in the absence of contraindications.

## Beta blockers

The use of beta blockers as primary BP lowering therapy

has been discouraged among diabetic patients due to its potential adverse metabolic effects, including an increase in triglyceride levels, a decrease in HDL cholesterol levels, weight gain, masking hypoglycaemia, and impairing insulin sensitivity.[11] In addition, it has been suggested that use of beta blockers in non-diabetic individuals, particularly those who are overweight or obese, might increase the risk for development of diabetes compared with an alternative agent. Beta blockers may still be used as add-on treatment in those who require multiple agents and in patients in whom another indication for the use of beta blockers is present, such as those with tachycardia, heart failure, or ischemic heart disease.

### Calcium channel blockers (CCBs)

CCBs are considered a potential first-line treatment for hypertensive diabetics, particularly in the elderly (age >55) with isolated systolic hypertension. CCBs have been shown to be particularly effective in the prevention of stroke, but are less effective than RAAS blockers in the prevention of heart failure.[12] Although, non-dihydropyridines decrease urinary protein excretion and serve as an alternative in RAAS inhibitor-intolerant patients. CCBs are ineffective for the prevention of diabetes in non-diabetic individuals. In summary, CCBs may be used as first-line agents for the treatment of hypertension in diabetic individuals, particularly in the elderly with isolated systolic hypertension.

### Diuretics

Although there has been concern that diuretics might increase the risk for the development of diabetes mellitus due to their potential to negatively influence insulin resistance, diuretics are important agents used for the treatment of hypertension in diabetics. In a sub-analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and SHEP trials, Chlorthalidone was found to be as good as Amlodipine or Lisinopril in preventing fatal and non-fatal coronary artery disease and was more effective in the prevention of heart failure in diabetic patients. Chlorthalidone or Indapamide were the main diuretics to be used for antihypertensive purposes.[13] To summarize, diuretics may be used for the treatment of hypertension in diabetics either as first line agents or as add-on treatment, but glucose and electrolytes should be monitored when initiating therapy.

### Alpha blockers

There are no specific studies which evaluated the efficacy of alpha blockers in diabetic patients. Although alpha blockers do not adversely affect glucose metabolism or lipid profile, but they have been reported to be less effective than diuretics for prevention of stroke and heart failure and therefore are used almost exclusively in patients with hypertension and prostate hyperplasia or as third or fourth-line agents.

### Aldosterone antagonists

Low dose Spironolactone was found to be effective in controlling BP in patients with hypertension and diabetes. The addition of Spironolactone is particularly effective in those with serum potassium of <4.5 mmol/L. The addition of Spironolactone to conventional antihypertensive treatment in diabetic patients and in diabetic patients with albuminuria, addition of an aldosterone antagonist to an ACEI has been shown to have renoprotective effects. Finerenone is a new non-steroidal anti mineralocorticoid having less adverse effects like gynaecomastia, impotence, low sex drive, and hyperkalemia. Addition of Finerenone to an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker improved urinary albumin-creatinine ratio better than placebo among patients with diabetic nephropathy.[14] It seems that aldosterone antagonists have a reno-protective effect that is independent of systemic hemodynamic alterations. Diabetic individuals tend to develop type 4 renal tubular acidosis and therefore hyperkalaemia may be a concern in those treated with aldosterone antagonists, particularly when combined with ACEIs or ARBs, an effect which must be monitored especially at the start of therapy.[15]

### Combination therapy

More than two-thirds of hypertensive individuals are inadequately controlled on mono therapy. Most diabetic individuals are treated with RAAS inhibitors and most guidelines recommend adding a calcium antagonist or diuretic as add-on therapy, with each having its own pros and cons as summarised in table 2.

Combining a RAAS blocker with a CCB provides better renoprotection and leads to less ankle edema compared with a CCB alone. In addition, combining an ARB with a CCB was associated with improved insulin sensitivity

**Table 2: Combination therapy in hypertension**

| | |
|---|---|
| **Target blood pressure** | <140/90 mmHg in most patients, consider <130/80 mmHg if additional risk factors for microvascular complications are present |
| **ACE inhibitors/ARBs** | First line therapy because of decreased cardiovascular risk with CAD |
| **Long acting thiazide diuretics** | Good cardiovascular risk reduction but slight increase in blood glucose |
| **Calcium channel blockers** | Good cardiovascular risk reduction and effective anti anginal |
| **Aldosterone antagonists** | Particularly effective in patients with prior MI or LV dysfunction. |
| **Beta blockers** | Do not reduce mortality in uncomplicated patients with stable CAD, choose vasodilating beta blockers for less adverse metabolic effects |

compared with an ARB and a diuretic. Based on these studies, it seems that CCBs are appropriate as second-line agents in diabetic patients already treated with RAAS blockers. In obese individuals or when volume overload is present, diuretics may be used as well. In patients requiring triple therapy, RAAS blockers should be combined with diuretics and CCBs, unless there is compelling indication for the use for a different anti-hypertensive class (heart failure or ischemic heart disease for beta blockers or benign prostate hyperplasia for alpha blockers). Patients with resistant hypertension, particularly in the presence of low potassium levels, may benefit from aldosterone antagonists. These should be used cautiously, particularly in patients already on RAAS blockers. The above discussion can be summarised as shown in figure 2 below. Once BP goal has been achieved, antihypertensive treatment should be continued. In the ADVANCE trial, discontinuation of antihypertensive medications was associated with increased risk of combined macro and microvascular events.

## Novel Anti-diabetes Medicines

In the last decade, there is an advent of new anti-diabetic medications working on different pathways of insulin production and glucose metabolism. Some of these agents do also have beneficial effects on BP and may prove as important agents for the control of hypertension in diabetic individuals. Hence, here we look for some of such agents and their effect on BP in patients with hypertension along with diabetes.

**Sodium-glucose-transporter 2 (SGLT2) inhibitors:**

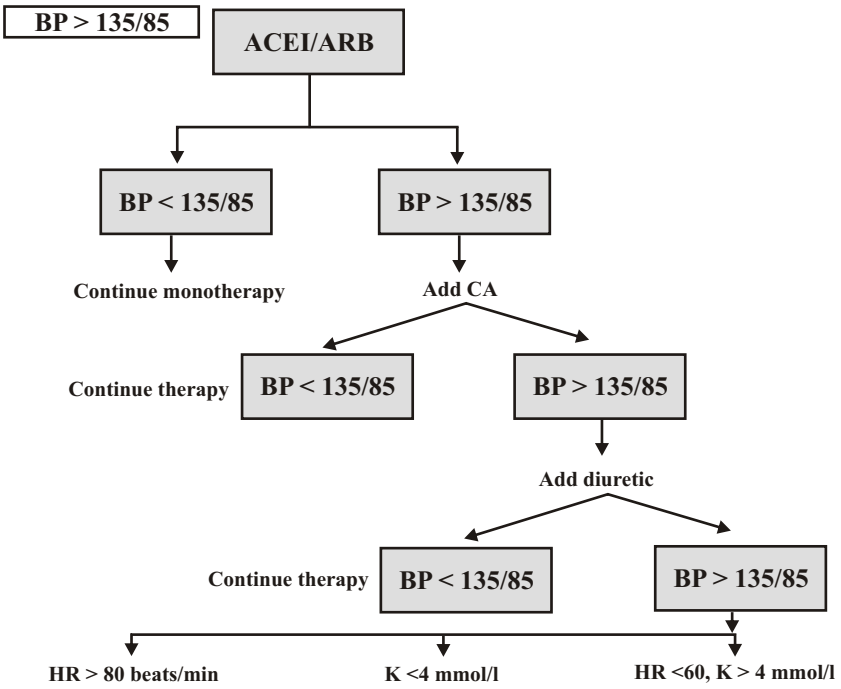


**Figure 2: Effective hypertension management cascade in diabetes.**

Three representatives of this new class of anti-diabetics are currently in the market Canagliflozin, Dapagliflozin, and Empagliflozin. All three have similar efficacy in terms of glucose control and all are associated with significant weight loss and have been reported to significantly decrease systolic and diastolic BP by 35/23 mmHg.[16] The mechanism underlying the BP decrease by SGLT2 inhibitors is unclear and potential mechanisms include diuresis, nephron remodelling, decrease in arterial stiffness, and weight loss. This class of agents is certainly promising as it can be used to control glucose, weight, and BP. In fact, the EMPA-REG trial indeed showed that Empagliflozin is associated with decreased CV morbidity, CV mortality, and overall mortality. Several potential non-glycemic mechanisms such as BP decrease and weight reduction have been suggested to explain the CV benefit of SGLT2 .Whether SGLT2 inhibitors can be used for BP control in non-diabetic individuals is unclear.

**Glucagon-like-polypeptide 1 analogues:** Glucagon-like-polypeptide 1 analogues (GLP1a) lead to a clinically significant weight loss in both diabetics and non-diabetics and thus may aid in a better BP control. On the other hand, they have been reported to increase heart rate through sympathetic nervous system activation and this may result in BP elevation. In the recently published Liraglutide Effect and Action in Diabetes: Evaluation of Cardio-vascular Outcome Results (LEADER) trial and in the trial to evaluate CV and other long-term outcomes with Semaglutide in subjects with Type 2 Diabetes (SUSTAIN-6) in which the CV safety of Semaglutide was evaluated, shows that GLP1a have a neutral effect on BP[17] and may even result in a mild decrease in BP, but probably cannot serve as an alternative to anti-hypertensive treatment in hypertensive diabetics.

**Dipeptidyl peptidase-4 (DPP4) inhibitors:** DPP4 inhibitors elevate endogenous GLP1 through inhibition of the endogenous substance responsible for its degradation. DPP4 inhibitors are neutral in term of BP control and their initiation probably does not significantly affect BP control.

## CONCLUSION

To reiterate, current evidence does not support a stringent BP control strategy for all diabetic patients and is mostly limited to patients with CV complications, also the evidence to support stringent control in certain diabetic patients is also inconclusive. In elderly diabetic patients (>80 years) BP levels should be less than 140-150/90 mmHg to prevent stroke in particular and should be monitored closely in the sitting and the standing position and the treatment should be tailored to prevent excessive fall/decrease in BP particularly taking into account the associated autonomic neuropathy. The choice of anti-hypertensive agent is supported by minimal evidence although RAAS blockers are usually used as first-line agents. When requiring more than one agent for the control of hypertension in diabetics, calcium antagonists or diuretics are probably appropriate as second line agents, followed by beta and alpha blockers, these agents can be used earlier in certain situations e.g. alpha blockers in associated BPH and beta blockers in patients with ischemic heart disease. New agents used for the treatment of diabetes may aid in the control of hypertension and a diagnosis of hypertension in a diabetic person may influence the clinician's choice to use a certain anti-diabetic treatment, but with limited conclusive evidences of benefits. In addition to lowering BP, it is very important to control all other risk factors in diabetic patients, in particular deranged lipid profile, obesity, smoking, alcohol intake to name a few. Hence a heterogenous treatment model answering the needs and wish of every patient should be framed and tried to be implemented on individual basis for better outcomes, particularly in patients with multiple comorbidities requiring long term treatment and hence more compliance.

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