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Systematic Review

Optimizing Cardiovascular Outcome in Type 2 Diabetes Mellitus with Better Control of Diabetes Mellitus with Empigliflozin and Hypertension with Renin Angiotensin System Inhibitors and Manidipine Preferably of the Dihydropyridones

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ABSTRACT

Aim: Obesity is increasing globally by leaps and bounds and thus the incidence of type 2 diabetes mellitus (T2DM) along with it so much so that the term diabesity had to be coined. Earlier we had reviewed how to treat the both together and the role of empagliflozin to improve cardiovascular outcome trials (CVOT). Similarly T2DM and hypertension are pathophysiologically-related diseases which co-exist with a broader complex of metabolic diseases which co-exist possessing similar set of risk factors. Hence it is important to consider which antihypertensives are suitable that possess a positive effect on metabolic factors in cases of T2DM who require an antihypertensive.

Method: A systematic review was carried out using the PubMed search engine with the MeSH terms: "T2DM"; "essential hypertension; "cardiovascular (CV)"; "Complications of diabetes mellitus (DM) and antihypertensive"; "Antihypertensive preferred in T2DM subjects"; "Renin-angiotensin–aldosterone system inhibitors"; "Angiotensin converting enzyme inhibitors (ACEi)"; "Angiotensin receptor blockers (ARBs)"; "Dihydropyridine calcium channel blocker"; "β2 blockers"; "Diuretics".

Discussion: Most diabetes mellitus (DM) subjects need a minimum of two antihypertensive drugs, combining a renin-angiotensin-aldosterone system (RAS) inhibitor with a dihydropyridine calcium channel blocker seems to be the most indicated approach. But not all dihydropyridine calcium channel blockers have equivalent effects on metabolic parameters. Hence manidipine that causes positive effect on insulin resistance (IR) seems to be an effective option. We have reviewed how manidipine is superior to amlodipine with regards to improving IR, not seen with amlodipine, along with not causing excessive sympathetic nervous system (SNS) activation, pulse pressure and ankle edema or to much lesser extent than amlodipine. Therefore, manidipine needs to be the first addition to RAS inhibitors in case of DM's having hypertension of the dihydropyridines calcium channel blockers. Further good blood pressure (BP) control been correlated with good CVs outcomes.

Conclusion: A RAS inhibitor is the first line of choice of drugs in a subject with T2DM who needs to be treated with empagliflozin for better CVOT outcome, and when a 2nd drug has to be added it is manidipine that is preferred over amlodipine. Plant products are proving to be having a lot of beneficial effects in DM, obesity and hypertension. Thus need for developing agents from plants will prove to be more cost effective in these chronic diseases where compliance is difficult to achieve with the use of common antiDM drugs and antihypertensives with the cost factor along with their side effects.

Keywords
Type 2 diabetes mellitus (T2DM); Diabesity; Antihypertensives; Renin-angiotensin-aldosterone system (RAS) inhibitor; dihydropyridines calcium channel blockers; Plant products.

INTRODUCTION

With increasing obesity there is simultaneous rise in co-morbidities like diabetes mellitus (DM) and hypertension (HTN), the commonest causes of cardiovascular diseases (CVD). While DM has more than 2-3 times increase in the incidence of ischemic heart disease in men than in women. The relative risk for CVD morbidity and mortality in adults with diabetes ranges from 1 to 3 in men and from 2 to 5 in women compared to those without DM as per Rivellese et al.[1,2] Other than DM, it has been seen that roughly 54% of stroke, 47% cases relating to coronary artery disease, with roughly 14% of mortality globally is attributed to arterial hypertension.[3] Analysis of data related to 11 researches involving 28,887 people between 35-74-years got included in which total prevalence of hypertension turned out to be 47% in men and 39% in women, and of DM 16% and 11% respectively.[4] Since instance of obesity are rising out of proportion and although only 171 million people having DM in 2000, the rough calculation for 2030 is 350 million.[5]

Between DM and hypertension a close association gets reflected by patients presenting with DM have a doubling of chance of hypertension, and conversely those individuals who had hypertension had a 2.5 times chance of developing DM.[6] Thus over 60% patients with DM have hypertension and with the acquisition of albuminuria incidence of hypertension goes up to 90%.[6] Further in patients of DM roughly 75% of cardiovascular system (CVS) outcomes are associated with hypertension.[1,7] On the presence of both further risk of CVS complications especially Coronary heart disease (CHD).[8] Hence controlling the risk factors control targets that is recommended in DM is the best method of preventing CVS risk in T2DM patients.[9]

Earlier we have concentrated on etiopathogenesis of obesity, ways of improving medical management of obesity over bariatric surgery, considering diabesity together for management of obesity and DM. This article is a review of how to effectively manage hypertension an important complication of obesity, that has an effect on cardiovascular outcome trials (CVOT) outcome of antidiabetic therapies[10-19] and further the advantages and role of manidipine over amlodipine addition to a renin-angiotensin–aldosterone system inhibitor is considered in detail.

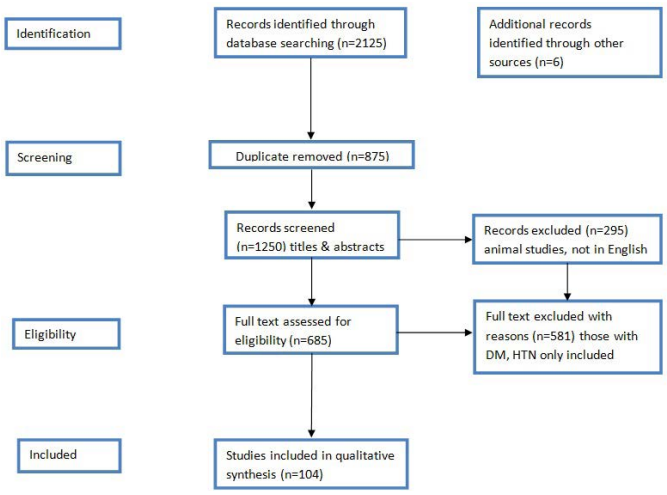
METHODS

A systematic review was carried out using the PubMed search engine with the MeSH terms: "T2DM"; "essential hypertension; "cardiovascular (CV)"; Complications of DM and antihypertensives"; "Antihypertensives preferred in T2DM Subjects"; "Renin-angiotensin-aldosterone system inhibitors"; "Angiotensin converting enzyme inhibitors (ACEi)"; "Angiotensin receptor blockers (ARBs)"; "Dihydropyridine calcium channel blocker"; "β2 blockers"; "Diuretics".

RESULTS

We found a total of 2131 articles out of which we selected 104 articles for this review. No meta-analysis was done. The articles chosen emphasized on treatment of obese subjects having both T2DM as well as hypertension (Figure 1).

Figure 1. *Overview of Literature Search with Inclusion Criteria*



n=number; DM-Diabetes mellitus; HTN-Hypertension

CAUSES OF HYPERTENSION IN DM

Of the multiple explanations given i) increased activation of the renin-angiotensin–aldosterone, ii) the sympathetic nervous system (SNS), iii) oxidative stress, iv) low-grade inflammation status and v) changes in the insulin–stimulated vasodilation, vi) impairment of innate and adaptive immunity, vii) abnormal processing of sodium by kidney viii) along with presence of nephropathy have been involved in causing both hypertension and DM.[20] How many of these factors operate in an isolated patient differs between subjects although all of these may contribute to the change in homeostatics of the patient.[20-22] Further the increase in adipose tissue (AT) and obesity have an impact on etiopathogenesis of DM and hypertension. The chronic low-grade inflammations, along with oxidative stress present in AT of obese subjects stimulate the activation of renin-angiotensin–aldosterone system.[10-13] Further viii) leptin that is an adipokine that is synthesized by AT is elevated in obese individuals, that stimulates the SNS.[20]

There is 50% presence of insulin resistance (IR) in hypertensive patients that causes damage to the vessels, which includes abnormal function, stiffness of vessels, hypertrophy, fibrosis and remodeling. Additionally, IR increases sympathetic output and aids in sodium reabsorption in the diluting segment of the distal nephron, causing reduced sodium excretion and ultimately higher blood pressure (BP) levels. Further IR also promotes renin-angiotensin-aldosterone system. Higher insulin volume along with sodium retention in the kidney along with activation of the SNS.[20-23] Conversely oxidative stress because of reactive oxygen species (ROS) synthesis helps in the development of further IR, DM along with hypertension.[20,23]

Activation of SNS is seen in cases of essential hypertension and DM. Though lot of factors are responsible for this,

like genetic influence, increased salt intake, sedentary lifestyle, with obesity being an important factor. Obesity helps in SNS activation *via* a lot of modes like i) increased–sodium–intake–associated methods, ii) cardiopulmonary reflex function abnormality, iii) renin-angiotensin–aldosterone system activation, iv) baroreflex abnormal function, v) chemoreceptor function abnormalities, vi) central factors, vii) changes in insulin, leptin amounts or ix) ROS, x) Nitric Oxide (NO) balance problems. This abnormality in the balance might get partly resolved by chronic intake of certain long acting dihydropyridine calcium channel blockers.[21,24-26] Increased platelet aggregation, with presence of abnormal balance between coagulation and fibrinolysis are other factors attributed to the procoagulant state that has been demonstrated in subjects of DM and hypertension.[2,20,21]

Use of Antihypertensive Agents in Subjects with T2DM and Hypertension

As per the United Kingdom Prospective Diabetes Study (UKPDS) in T2DM, it was demonstrated that once 10 mmHg systolic blood pressure (BP) reduced, a decrease in complications of DM by 12% (p<0.0001), decrease in mortality related to DM by 15% (p<0.0001), with microvascular side effects by 13% (p<0.0001), reduced myocardial infarction (MI) by 11% (p<0.0001). What was important was that decreasing BP had more benefits with regard to CVS events than glycaemic control per se.[27]

Although the observational studies have indicated that the lesser, the better for BP in DM, only benefits seen on macro and microvascular side effects once decrease BP upto <140/90 mmHg in DM as per randomized controlled trials (RCTs). Moreover in certain high-risk hypertensive patients with DM, increased fall in BP might cause harm.[28] Like in ACCORD (Action to Control Cardiovascular in DM trial), where 4,733 subjects with T2DM got randomized to a systolic BP goal <120 mmHg (intensive therapy) or <140 mmHg (standard therapy), the risk for the primary outcome was same in both groups following a mean follow-up of 4.7-years. But aggressive therapy was correlated with decreased risk of stroke (HR 0.59; 95% CI 0.39-0.89), but with increased risk of serious side effects secondary to antihypertensive agents.[29] Lower total mortality risk (RR 0.73; 95% CI 0.53-1.01), was observed in another study that evaluated 5 clinical trials, where decrease of BP (128/76 *vs* 135/83 mmHg) in cases of DM was achieved.[30] In view of that the BP targets have been reconsidered in patients with both DM and hypertension.[28] Thus in contrast to the earlier recommendations of BP < 130/80 mmHg for diabetics, recent recommendations are a BP target of <140/85 mmHg (European Society of Hypertension/European Society of Cardiology) or <140/90 mmHg (Eigth Joint National Committee and American Society of Hypertension/International Society of Hypertension.[31,32] Contrary to that epidemiological studies have revealed that though the last year BP control has become better, the actual fact is that a less number of subjects having hypertension and DM do not achieve BP goals at present.[33]

Though all first line antihypertensive drugs decrease BP similarly, and thus can be used in DM, it has been seen that renin-angiotensin–aldosterone system inhibitors give added benefits on both CVS along with renal outcomes beyond only BP regulation in these subjects.[26-28] Meta-analysis carried on 10 RCT studies having a total of 21,871 subjects with hypertension and T2DM which evaluated the effects of Angiotensin-converting-enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) on CVS events demonstrated that the total treatment with ACEi/ARBs markedly decreased the risk of CVS events by 10% and risk of CVS deaths by 17%.[34]

Further therapy using ACEi/ARBs has been observed to help in avoiding or minimal delay the formation of nephropathy in subjects with T2DM. Hence in a meta-analysis comprising of 28 studies, where 18 studies ACEi/ARBs *vs* active drugs, 31 comparisons and 13 studies compared ACEi/ARBs *vs* placebo, 20 comparisons as compared to other antihypertensives, inspite of similar decreases in BP, therapy with ACEi/ARBs was correlated with marked reduction in risk of serum creatinine doubling along with macroalbuminurea. Further the number of patients who demonstrated albuminurea disappearance were more in patients treated with ACEi/ARBs. Additionally a lesser chance of end-stage renal disease and microalbuminuria was seen in the ACEi/ARBs group.[35] But use of ACEi or ARBs is of special use, various clinical trials have shown combining the two needs to be avoided, as no benefit is seen with more chance of side effects.[36] Hence unless contraindicated every subject with T2DM with hypertension should be treated with a ACEi or an ARB.[31,32]

Nevertheless it has been shown that approximately 75% of subjects of T2DM with hypertension will need a minimum of 2 antihypertensives for attaining the BP target.[33-36] Earlier traditions involved in maximum cases use of a renin-angiotensin–aldosterone system inhibitor along with a thiazide–like diuretic or a calcium channel blocker. But avoiding cardiovascular events in combination therapy in patients living with systolic hypetension (ACCOMPLISH) trial demonstrated in 11,506 subjects who were high-risk hypertensives that combination of an ACEi with a dihydropyridine calcium blocker decreased the risk of CVS events when compared with ACEi along with a hydrochlorothiazide.[37] These results were counter checked in the subgroup of patients having T2DM. Hence in this subgroup in contrast to hydrochlorothiazide group the combination with the calcium blocker decreased the risk of CVS death, MI, stroke, hospitalization secondary to angina, resuscitated arrest and coronary revascularization by 21% (HR 0.79; 95% CI 0.68-0.92, p=0.03). Importantly coronary events along with revascularization were decreased in those subjects treated with ACEi with a dihydropyridine calcium blocker.[38] Thus if combined therapy needed for treating T2DM with hypertension, a combination of renin-angiotensin–aldosterone system inhibitor with a dihydropyridine calcium blocker needs to be given preference.

Calcium Channel Blockers in T2DM with Hypertension

In all calcium channel blockers decrease BP with efficacy, and tolerated well. They get used for T2DM with hypertension with great frequency. Like in Reduction of Endpoints in NIDDM with

the Angiotensin II Antagonist Losartan (RENAAL) study, where 1,513 subjects with T2DM and nephropathy got randomized for losartan/placebo besides receiving conventional antihypertensives, approximately 80% of patients in both groups were given calcium channel blockers for getting the BP targets.[39]

Most of the studies have evaluated the actions of calcium channel blockers on CVS outcomes in subjects with T2DM with hypertension. In the appropriate blood pressure control in diabetes (ABCD) study, as compared with enalapril, therapy with nisoldipine, correlated with markedly there are more chances of fatal along with non-fatal MI, of these patients who were cases of non-insulin DM and hypertension.[40] In case of fosinopril *versus* amlodipine cardiovascular events randomized trial (FACET) study, although BP got decreased to the same amount, with no variations in total serum cholesterol, high-density lipoprotein (HDL) cholesterol, hemoglobin A1C (HbA1c), fasting serum glucose or plasma insulin between groups, those subjects who were randomized for receiving fosinopril had significantly reduced chances of any major vascular problems, in contrast to those getting amlodipine in cases of non-insulin DM and hypertension.[41] Conversely in irebesartan diabetic nephropathy trial (IBNT), where 1,715 adult subjects having diabetic nephropathy and hypertension were randomized for getting irebesartan, amlodipine or placebo besides receiving conventional antihypertensives, time till CV death, MI, congestive heart failure (CHF), strokes and coronary revascularization happened similarly in the 3 groups. But in those getting amlodipine showed significantly decreased rate of MI as compared to placebo (HR 0.58; 95% CI 0.37-0.92; p=0.02).[42] In the huge subgroup of subjects with DM (n=5137) that were included in the BP decreasing arm of anglo-scandinavian cardiac outcome trial (ASCOT) study those getting amlodipine based therapy (where perindropil addition could be done if needed) correlated with a decrease in the incidence of the composite endpoint of total CVS events along with procedures, as compared with atenolol based regimen (thiazide could be given if needed) (HR 0.86 95% CI 0.76-0.98; p=0.026). Additionally, amlodipine based therapy was correlated with decrease in fatal and non-fatal strokes, peripheral arterial disease (PAD), and noncoronary revascularization.[43]

From these data it is clarified that although renin-angiotensin–aldosterone system inhibitors need to be considered to be the 1st line therapy for treating subjects who were cases of DM and hypertension, when a 2nd antihypertensive is needed for achieving BP control, it needs a calcium channel blocker with a renin-angiotensin–aldosterone system inhibitor has been demonstrated to be possessing complementary modes of action which increase their efficacy, with low chance of side effects.[2,44]

Role of Metabolic Control in T2DM with Hypertension

For CVS risk reduction in all in cases of DM, best method is the comprehensive management of all CV risk factors. But some antihypertensives might cause effects on metabolic parameters that are not favourable and need to be used only when the indication is very high, and are avoidable in subjects of DM or at risk of developing DM, like patients having metabolic equivalents (METs). In contrast those anthypertensives displaying a neutral/favourable metabolic parameters are the ones required to be used in such subjects preferably.[2,45]

As per many works renin-angiotensin–aldosterone system inhibitors display good effects on the glucose homeostasis. In a meta-analysis, that evaluated the actions of renin-angiotensin–aldosterone system inhibitors on the chances of new onset DM, 10 RCTs (8 regarding hypertensive population and 2 in heart failure patients) were the inclusion criteria. While 7.4% of patients getting ACEi or an ARB, had showed new onset DM, that happened in 9.63% of controls (relative risk reduction 22%; 95% CI 18-26%; p<0.00001). This effect that was of benefit was same irrespective of the type of renin-angiotensin–aldosterone system inhibitor utilized (ACEi or an ARB), the type of comparison drugs (placebo or beta blockers/diuretics or amlodipine) or the king of basic condition (hypertension, heart failure).[46] In another recent meta-analysis it has been demonstrated that ACEi decreases the chances of new onset DM in comparison with beta blockers/diuretics by 22% and with calcium channel blockers by 15%.[47] Same group observed in another meta-analysis, a reduction in new onset DM with use of ARB as compared with beta blockers/diuretics by 27%, and placebo by 12% and with calcium channel blockers by 24%.[48] This data is not astonishing in view of renin-angiotensin–aldosterone system having a crucial part in the etiopathogenesis of both hypertension and metabolism of glucose.[45]

Into a calcium channel blockers possess a neutral effect on metabolism of glucose. Hence a meta-analysis of 10 RCT, in which 108,118 hypertensive subjects with preexisting DM, calcium channel blockers correlated with a increases the chance of DM in contrast to ACEi or ARB, but with lesser chance in comparison with beta blockers/diuretics.[49] Same results have been obtained from other meta-analysis.[50] Yet not all calcium channel blockers possess the same effects on metabolism of glucose, like some researchers demonstrated azelnidipine could abrogate IR.[51] But the results got from manidipine on benefitting in IR have more consistency.[52,53]

In contrast, in aggregate, beta blockers/diuretics are shown to possess unrewarding results as far as glucose homeostasis is concerned.[48] Actually various studies have demonstrated that therapy with beta blockers causes higher chances of DM development. A Meta-analysis involving 94,492 subjects with hypertension getting therapy with, beta blockers, enhanced risk of new onset DM by 22% (RR 1.22, 95% CI 1.12-1.33) in comparison to non-diuretic antihypertensives. Risk of DM was increased with atenolol.[54] But not all beta blockers are harmful with regard to glucose homeostasis. Most of the studies have revealed that beta blockers like bisopropol, carvedilol or nebiviol might not affect glucose homeostasis in a negative way.[55]

All over the world diuretics enhance the risk of new onset DM. Hence in a meta-analysis, where 48 randomized groups out of 22 clinical trials that involved 143,153 subjects, not having DM at the time of randomization, the chance of DM with antihypertensives was least ARB and ACEi followed with calcium channel blockers and placebo beta blockers and diuretics in this

order.[56] But just like with beta blockers, all diuretics don't have the similar effect on glucose homeostasis. Hence it appears possibly chlorthalidone's metabolic profile might be helpful in contrast to other thiazide or thiazide like diuretics.[45,57] Other workers revealed that amiloride and hydrochlorothiazide decreased BP to a similar amount, therapy with hydrochlorothiazide was related to escalation of glucose levels following a 2-hours glucose tolerance test but not with amiloride.[58] In case of eplerenone in mild patients hospitalization and survival study in heart failure (EMPHASIS-HF) study tried to evaluate the efficacy of Eplerenone along with conventional therapy on clinical results in 2,737 subjects with systolic heart failure and mild symptoms in those subjects with DM at baseline (n=1846), Eplerenone did not enhance the chances of new onset DM (HR 0.94, 95% CI 9.59-1.52).[59]

Arterial Hypertension and Adrenergic Tone

In the pathophysiology of hypertension, along with metabolic control SNS plays a crucial role. Chronically enhanced sympathetic tone helps in increasing formation of obesity, hyperglycemia, IR and hypertension.[21,24,60] Further escalated sympathetic activation system might enhance pulse pressure. Its relevance is demonstrated by poor correlation of more than than pulse pressure with worst CVS prognosis is seen.[61]

First development of dihydropyridine calcium channel blockers had the characteristic of rapid release, and short lifetime, with rapid absorption. Hence tachycardia with sympathetic activation was prevalent. In contrast last generation of dihydropyridines have the properties of long life and thus prolonged action, resulting in low sympathetic activation. Hence these latter drugs possess better CVS along with tolerability profiles.[52,53] Inspite of this it is not that all 3rd generation dihydropyridine calcium channel blockers have similar action on sympathetic activation.[62,63]

Further Benefits of Manidipine on BP Control

A third generation dihydropyridine calcium channel blocker, manidipine reduces BP levels with a maintainance of effect over 24-hours, without any significant hydroxyethylrutosides (HR) rise or cardiac output increase.[64] Variety of studies have evaluated the antihypertensive efficacy of manidipine.[62,63,65-70] As per these studies manidipine decreases levels of BP in an equivalent way to enalapril, lisinolipril, or amlodipine, of the other antihypertensives. Hence in a study carried out in T2DM and hypertension, following 24-hours of therapy 10 mg manidipine and 10 mg enalapril decreased BP levels equally (-23/-13 and -20/-12 mmHg, respectively. $p<0.01$ *vs* baseline; p=NS between groups.[65] A European randomized double blind, multicentre and parallel group (MAISH) study had 195 subjects ≥60-years-old, having isolated systolic hypertension got manidipine 10-20 mg once daily or amlodipine 5-10 mg once daily. Chlorthalidone 25 mg once daily could be added in case of uncontrolled BP inspite of high dose manidipine or amlodipine therapy. Following 12-weeks of therapy same decreases in systolic BP got seen in both groups (-19.5 and-18.4 mmHg, respectively; p=NS). Another meta-analysis that included 4 RCT's head to head of minimum 12-months of therapy that compared the effectiveness of 20 mg manidipine with that of 10 mg amlodipine therapy, 838 subjects got evaluated (for 20 mg manidipine group (n=436), for amlodipine group (n=402). An equivalent antihypertensive efficacy was observed for both (for diastolic BP effect size=-0.08 and for systolic BP=-0.01(p=NS for both systolic and diastolic BP).[69] From all the above results, it is clear that as monotherapy manidipine is efficacious. But many studies have illustrated that manidipine could be utilized as add on therapy, especially to renin-angiotensin–aldosterone system inhibitors. Hence in non-comparative along with open label study 136 subjects having T2DM with unregulated hypertension inspite of combined low dose diuretic with ACEi or ARB, supplementation of manidipine 10-20 mg/day decreased BP by roughly -22/-9 mmHg ($p<0.001$) following 6-months of therapy.[71]

A common side effect of DM and hypertension is microalbuminurea. Importance of this lies in the marked correlation of microalbuminurea with higher CVS risk.[31] Decreasing BP to recommended goals is essential for decrease of urine albumin excretion rates, some antihypertensives have revealed more benefits that goes further than only BP regulation. Related to this ACEi or ARB, and not both at the same time, remain the drugs preferred for treating patients with DM and hypertension, especially those presenting with microalbuminurea.[31,32] Comparison of combination of benazepril with hydrochlorothiazide in the ACCOMPLISH trial demonstrated that the earlier antihypertensive therapy using benazepril with amlodipine reduced the progression of of manidipine nephropathy to a higher amount.[72] This matches the results of a study demonstrated in a hypertensive group of subjects having DM microalbuminurea along with unregulated BP inspite of therapy with candesartan, where in comparison to adding hydrochlorothiazide 12.5 mg/day further addition 10 mg/day decreased urine albumin excretion rates upto a higher rate inspite of similar BP decrease.[69]

But importantly not all calcium channel blockers provide the similar renal protection. The situation is, as per variety of studies in hypertension with or without DM, that manidipine results in greater renal protection, in comparison to amlodipine, inspite of equivalent BP decrease, either alone or in addition to renin-angiotensin-aldosterone system inhibitors.[62,63] Hence evaluation of AMANDHA study utilizing multivariate analysis, the treatment that had been compared (manidipine *vis-a-vis* amlodipine) showed an independent correlation with alterations in urine albumin excretion.[73] These variations get understood by that amlodipine blocks only L-type calcium channels, while manidipine blocks both L- and T-type calcium channels. L-type receptors are only situated in the afferent arterioles but not in efferent arterioles. Hence on blocking L-type calcium channels, vasodilation gets limited to afferent arterioles, which ends in glomerular hypertension and hence as a result increased urine albumin excretion. In comparison T-type calcium channels being present in both afferent and efferent arterioles, blocking these receptors ≥ vasodilation of both arterioles, thus causing a decrease in intraglomerular pressure and hence decreased urine albumin excretion rates.[62,74-76]

The most common adverse effect of dihydropyridones is ankle oedema. Cause of ankle oedema with dihydropyridones calcium channel blockers, is a rise in intracapillary pressure, because

of selective enhancement of postcapillary tone due to sympathetic activation. As not all calcium channel blockers have similar action causing sympathetic activation, risk of ankle oedema might differ between a variety of dihydropyridones. Thus a meta-analysis, where amlodipine was compared with manidipine, a 65% lower risk of development of ankle oedema (RR 0.35; 95% CI 0.23-0.54; risk difference 11.3; 95% CI 7-16%) was there. Further as renin-angiotensin–aldosterone system inhibitors dilate the arteriolar vascular bed and venous capacitance vessels, that cause a decrease in intracapillary pressure, adding renin-angiotensin–aldosterone system inhibitors with dihydropyridones calcium channel blockers might decrease the ankle oedema related to dihydropyridones.[44,62] Hence in a study which included patients with untreated hypertension, adding delapril to manidipine, in part had a counter effect on the microcirculatory effects caused by manidipine that led to oedema. In this 3-way crossover study, in 3 subjects clinically appreciable ankle oedema were following manidipine monotherapy, and 1 patient with the combination of delapril and manidipine.[68]

Metabolic Effects of Manidipine

Several studies have pointed that manidipine improves insulin sensitivity by helping in the development along with differentiation of adipocytes, along with retaining peroxisome proliferator-activated receptor-gamma (PPAR-γ) action.[52,53,77] These have been demonstrated with manidipine in both when used as monotherapy, along with use in combination with renin-angiotensin–aldosterone system inhibitors.

Evaluation of metabolic effects of 10 to 20 mg manidipine once daily for 12-weeks was carried out in an open label and non-comparative study demonstrated in 102 cases of stage I-II essential hypertension from both sexes. No changes in metabolic parameters like fasting plasma glucose, total high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, triglycerides along with insulin sensitivity index was observed significantly.[78] Another study conducted in hypertensive subjects ≥ 70-years, therapy with manidipine for 6-months was not correlated with changes in glucose or lipid parameters, though a pattern of decreased triglycerides levels was seen.[79]

Japanese essential hypertension patients with non-insulin dependent DM were treated with manidipine or delapril for 3-months, that was an open trial, in which an improved insulin sensitivity index along with glucose effectiveness was seen. Further no differences between plasma glucose, total cholesterol and triglycerides or lipoprotein cholesterol fractions along with body weight was observed.[80] A multicenter trial that was double-blinded tried to find the difference in effectiveness along with safety profile of manidipine and enalapril in patients presenting with T2DM with hypertension for 24-weeks demonstrated marked decreases in HbA1c from 6.7% to 6.2% and blood glucose levels from 152 to 143 mg/dL, only in the manidipine group (p<0.05). No significant alterations were seen regarding other metabolic parameters.[65]

Actions of combination of manidipine with ACEi on insulin sensitivity and metabolic inflammatory and prothrombic, markers were evaluated in the MARCADOR study. This study possessed a prospective randomized open, blinded end-point (PROBE) design, where 120 subjects ranging from 35-75-years having stage I-II essential hypertension along with MetS were randomized to get either amlodipine 10 mg, temisartan 80 mg, manidipine 20 mg or manidipine 10 mg with lisinopril 10 mg. Following 14-weeks of therapy in contrast to amlopdipine, manidipine 20 mg, this group had a significantly better efficacy on IR (-26.5% *vis a vis* -3.0%), LDL cholesterol (-6.8 *vis a vis* +1.7%) and other metabolic factors. While manidipine correlated with slight rise in insulin sensitivity than manidipine with lisinopril, this combination had much greater efficacy regarding improvement of other metabolic factors from amlodipine, temisartan, manidipine combination.[81] MARIMBA Study had 64 patients without DM but having MetS, along with impaired fasting glucose (>5.6 nmol/l) and hypertension, had a randomization for manidipine 20 mg or amlodipine 10 mg for 12-weeks. Although equal decrease in BP was observed with both, plasma adiponectin, (that reflects inverse correlation with the formation of IR and MetS) was enhanced (32.9%; p=0.011) and plasma TNF-α was decreased by manidipine (-37.1%; p=0.019), but no significant alteration occurred in either with amlodipine, the HOMA insulin resistance index was decreased by manidipine significantly (-21.3%; p=0.007) but not through amlodipine (-8.3%, p=0.062).

Regarding the AMANDHA study, effectiveness, with safety of addition of manidipine 20 mg or amlodipine 10 mg over and above the treatment of subjects having DM and uncontrolled hypertension with microalbuminurea, inspite of treatment using whole dosage of a renin-angiotensin–aldosterone system inhibitor for 6 months mimimum got evaluated by both therapies. Equivalent reduction of BP took place with both.[62] Post adhoc evaluation, insulinization rates and alterations in insulin dose during the study got examined. Oral antidiabetic use and insulin got adjusted during the study as per the local practice. HbA1C at baseline was 8.1±1.1% in the manidipine group 8.2±1.0% in amlodipine one. Following 2 years of therapy was 7.6±1.3% and 7.9±0.9% respectively (p=NS). 72.2% patients treated with manidipine and 73.3% treated with amlodipine were receiving insulin therapy. Of these dosage of insulin was 0.47±0.13 U/Kg and 0.44±0.16 U/Kg respectively. Following 2 years of therapy insulin dosage was 0.36±1.1 U/Kg and 0.51±1.7 U/Kg respectively (p[manidipine *vs* baseline]=0.031; p[manidipine *vs* amlodipine=0.012]). Additionally, of those not getting insulin therapy at baseline, 11.8% of patients of manidipine group and 50% of those from amlodipine one had to initiate insulin therapy during the study (RRR 76.4% absolute risk reduction 38.2%; odds ratio 7.5)

Fogari R et al compared the actions of manidipine with dalapril *vis a vis* olmesartan/hydrochlorthiazide combination treatment in old patients with DM and hypertension, and randomized 158 subjects to get 10 mg manidipine with 30 mg dalapril or 20 mg olmesartan with 12.5 mg hydrochlorthiazide for 48-weeks duration. Once the study finished, inspite of similar decrease in sitting BP, no alterations in metabolic profile was seen with manidipine with dalapril, a rise in HbA1c (±0.4 mg/dL; p<0.05), and triglycerides (+41.3 mg/dL; p<0.05), and decrease in HDL-Cholesterol (-3.4 mg/dL; p<0.05), were observed in olmesartan/hydrochlorthiazide Group.[82] Another study carried out in 88 obese hyper-

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tension subjects, manidipine with dalapril group but not olmesartan/hydrochlorthiazide group significantly reduced IR along with plasma fibrinogen levels, inspite of similar BP reducing effectiveness.[83] One more study by Kohlmann et al. In patients with DM and hypertension with microalbuminurea, showed that while BP reducing effectiveness was equivalent in both groups following 1-year of follow-up, a pattern of decrease in blood glucose levels from baseline with manidipine with dalapril group (mean change -0.2 mmol/L; p=0.064), but not with losartan/hydrochlorthiazide combination.[84]

Further there are reports regarding strong statins having the capacity to help in DM development.[85] Liberopoulos et al[86] tried comparing manidipine 20 mg with rosuvastatin 10 mg with olmesartan 20 mg with rosuvastatin 10 mg on markers of IR in subjects having dyslipidemia, hypertension and impaired fasting glucose 3 months of therapy, significant enhancement of HOMA-IR index by 14% (from 2.4 to 2.7; p=0.02 *vs* baseline) was documented for olmesartan with rosuvastatin, while no significant alteration was found with manidipine with rosuvastatin (1, 7 to 1.7, p=NS *vs* baseline, p=0.04 *vs* olmesartan with rosuvastatin group). Additionally, increased fasting insulin was seen in olmesartan with rosuvastatin group (from 10.1 to 10.9 μU/mL; p<0.05 *vs* baseline) but not with manidipine with rosuvastatin (from 7.3 to 7.59 μU/ml; p=NS *vs* baseline, p=0.02 *vs* olmesartan with rosuvastatin group). No changes in fasting plasma glucose or glycosylated haemoglobin was seen in either group. Thus this reveals that manidipine abrogates the probable statin–related enhancement of IR in comparison with olmesartan.[86]

A study particularly having a design for evaluating the action of various dihydropyridine calcium channel blockers (amlodipine 5-10 mg, felodipine 5-10 mg, lacidipine 4-6 mg and manidipine 10-20 mg), for 24-weeks on plasma norepinephrine in essential hypertension subjects, a significant elevation in plasma norepinephrine concentration were seen with amlodipine and felodipine (+34.9% and +39.4% respectively; p<0.001 *vs* placebo) but not with lacidipine (+7.1%; p=NS) and manidipine (+2.9%; p=NS).[87] Conversely, a study comparing actions of manidipine with dalapril and irbesartan–hydrochlorthiazide combinations on fibrinolytic action in hypertension subjects with T2DM, where although manidipine with dalapril combinations increased fibrinolytic action, this function was worsened with irbesartan –hydrochlorthiazide combinations.[88] Variations in SNS activation stimulated with chronic therapy with dihydropyridine calcium channel blockers along with various functions on fibrinolytic function might affect the CVS outcomes. Actually studies showed that simvastatin with manidipine interaction a positive way in heart protection from ischemia-reperfusion injury.[89]

Lastly, as variations in sympathetic excessive activation following arterial vasodilation have been demonstrated to have variations in ankle oedema rates, calcium channel blockers which activate SNS to a minimum amount might cause less chance of ankle oedema.[61] This is observed with manidipine in contrast to amlodipine.[90]

ONTARGET/TRANSCEND TRIALS

Further in the ONTARGET/TRANSCEND studies, Bohm et al identified 11,487 patients with DM or without DM19450 patients out of a total of 30,937 subjects, picked up from 133 centres from 44 countries, having a median follow-up of 56-months. These patients had a history of stroke, MI, PAD or were high-risk diabetics. Patients in ONTARGET were randomized to ramipril 10 mg, telmisartan 80 mg daily, or the combination of both. Patients in TRANSCEND were intolerant to ACE and thus randomized to telmisartan 80 mg daily or matching placebo. Evaluation of association of mean achieved initial systolic blood pressure (SBP) and diastolic blood pressure (DBP) with composite outcome of CV death, MI, stroke and hospitalization for CHF, the components of the composite, and all cause death. In patients with DM, event rates were higher across the whole spectrum of SBP, and DBP as compared to those without DM (p<0.0001 for the primary composite outcome, p<0.01 for all other events). Mean achieved in trial SBP≥160 mmHg was related to an enhanced risk for the primary outcome [DM/No DM; adjusted HR 2.31 (21.93-2.76)/1.66 (1.35-2.02)] compared with non DM with SBP 120 to <140 mmHg], with equivalent observations for all other endpoints in patients with DM, and for MI and stroke in patients without DM. Initial SBP < 120 mmHg correlated with greater risk for the combined outcomes in patients with DM [HR 1.53 (1.27-1.85)], and for CV death and all cause death in all patients. Intrial DBP ≥ 90 mmHg correlated with higher risk for the primary outcome [DM/No DM: HR 2.32(1,91-2.82)/1.61(1.35-1.93) as compared with non-DM with BP 70 to <80 mmHg], with equivalent observations for all other endpoints, but not for CHF hospitalizations in patients without DM. Initial DBP<70 mmHg correlated with >risk for the combined outcomes in patients (DM/No DM:HR1.77 (1.51-2.06)/1.30(1.16-1.46)), and also for all other endpoints except stroke. Thus concluding treatment BP levels (≥160 or ≥90 mmHg correlated with hgher risk of CVS outcomes and death. Further even low-levels (<120 or <70 mmHg correlate with higher CVS outcomes (except stroke) and death. Subjects with DM possess consistently higher risks over whole BP range, that suggests that optimal BP goals has biggest impact in this group. These results favour guidelines taking lower BP boundaries into consideration, especially in DM.[91]

DISCUSSION

T2DM with hypertension subjects demonstrate a high CVS risk.[1-3] The American Diabetes Association (ADA) guidelines give a target of 140/90 mmHg for subjects with T2DM (A is the level of recommendation) but a value of <130/80 mmHg is alright for some diabetics having higher risk of CVD, if attained without any treatment burden (level of recommendation C).[92] A lot of subjects with T2DM with hypertension don't achieve these BP targets.[29,30] Actually most of subjects with T2DM with hypertension will need a minimum of 2 drugs for reaching these BP targets.[33,93] The ADA guidelines distinguish recommendations on the basis of CVD risk. High-risk subjects with T2DM need to have a BP<130/80 mmHg while subjects having low CVD risk need to have a BP>140/90 mmHg.

A practical method is needed to decrease risk of CVS in T2DM.[2,45] Thus in these subjects preferably use of antihypertensives drugs which have shown a positive action on metabolic factors. Thus utilization of an ACEi or ARB, but not the two together is important[26,92,94] following the ACCOMPLISH Trial, further use of dihydropyridine calcium channel blockers as add on therapy is recommended on need.[37,38]

But not all dihydropyridine calcium channel blockers are equivalent as far as their effects on metabolic factors are concerned. Manidipine has a positive action on these metabolic factors, helping in reducing insulin dosage in contrast to amlodipine.[68] Additionally, manidipine has positive actions regarding oxidative stress has been documented.[94] Far less SNS activation, thus lower metanephrines, HR, PR, ankle oedema and better in DM with MetS.

The ONTARGET/TRANSCEND studies, in large number of subjects showed that with DM, Bohm et al showed that BP levels (≥160 or ≥90 mmHg correlated with higher risk of CVS outcomes. Further even low-levels (<120 or <70 mmHg correlate with higher CVS outcomes (except stroke) and death. Subjects with DM possess consistently higher risks over whole BP range, that suggests that optimal BP goals has biggest impact in this group. These results favour guidelines taking lower BP boundaries into consideration, especially in DM.

CONCLUSION

Therefore, the drug of choice in subjects presenting with T2DM with hypertension remain renin-angiotensin–aldosterone system inhibitors. If a 2nd antihypertensive is required, a dihydropyridine calcium channel blocker needs to be opted for, where manidipine is a much better choice in contrast to amlodipine. Gupta et al analyzed prescriptions in consecutive patients with T2DM at 9 sites in India, of which hypertension therapy details were available in 8056 of 8699 subjects (n=4829 men, n=3227 women), no hypertension was present in 3300 (40.9%) hypertension in 3625 (45.0%) hypertension with vascular disease in 1131(14.0%). In DM patients having no hypertension, hypertension and hypertension with vascular disease, respectively prescription in antihypertensives drugs was: renin-angiotensin–system (RAS) blockers in 19.4, 48.2 and 58.1%, beta blockers in 4.8, 31.6 and 38.8%, calcium channel blockers in 0.4, 27.4 and 14.3% and diuretics in 0.6, 36.4 and 17.1%. ACEi were prescribed is more than ARB's in hypertensive diabetics (60.7 *vs* 39.2%) along with in DM patients having vascular disease (58.6 *vs* 41.4%). In DM with hypertension (n=3625), prescription of 1, 2 or 3 antihypertensives drugs was 49.8%, 33.7% and 3, 5%, while statins was prescribed in 54.1%. Thus they demonstrated that use of ACEi or ARB's in both uncomplicated hypertensives patients with T2DM remains suboptimal. Most of the patients are on 1 drug and prescription of ≥ 3 drugs are rare with statins being prescribed only in 50% subjects.[96] This is one example of how >2 antihypertensives are not being used currently in most of the world, which needs, emphasis. Like we had earlier emphasized on the importance of use of empigliflozin in treatment of T2DM for a better CVOT,[97] similar results have been emphasized by the EMPRISE study results.[98] Huang et al in a retrospective study on the risk of new onset DM (NOD) with antihypertensive drugs found that after adjusting all parameters, risk of NOD was highest with thiazide diuretics and nondihydropyridones CCB's were at higher risk of developing NOD in Taiwan.[99] Further as we have been emphasizing on the use of plants products like monoterpenes and other plant products like PTB Inhibitors (unpublished observations), Chukwama et al reviewed 64 studies with plant species that matched there selection criteria. Members of the *Fabaceae* family were the most investigated plants, while the ω greatly varied across the plants, with only 11 plants having a ω=1. *Withania somnifera Dunal* was the only plant reported to show blood glucose lowering and diuretic effect in humans compared to daonil. Caffeic acid, chlorogenic acid, caftaric acid, cichoric acid, verbascoside, leucosceptoside, fucoxanthin and nicotinamide were the reported dual acting antidiabetic and antihypertensive compounds pointed and/or isolated in the plants. Thus suggesting that medicinal plants have different therapeutic dynamics against hypertension and DM which might get exploited to discover therapeutic preparations/agents to treat both diseases.[100] Limitations of the study is that we have mainly studied obese diabetics and hypertensives. Best option of treatment would be the 4th generation calcium channel blocker (CCB), Cilnidipine with Ace inhibitors or ARb'S.[101] Already we have started using the 4th generation CCB, Cilnidipine in our antenatal patients with Pregnancy-induced hypertension (PIH) in view of non-availability of labetolol and are carryimg out double blind trials to study them and need to further study it and start using it in diabetic hypertensives instead of amlodipine being currently used. Further with the advent of 4th generation CCB Cilnidipine with ACEi were detected to have an edge over nephroprotection, reducing microalbuminurea and reduction of symphathetic activity. Therefore, more trials are required with combining Cilnidipine with ACEi or ARB's in hypertensive diabetics with or without obesity[102,103] with double blind trials all over world with regards to use of these 2 combinations together to reduce SNS metabolic complications along with reduction of insulin dosage. Thus, right now best treatment recommended is enalpril with cilnidipine as one example or other ACEi or ARB's with cilnidipine.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Leon BM, Maddox TM. Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes*. 2015; 6: 1246-1258. doi: 10.4239/wjd.v6.i13.1246

2. Barrios V, Escobar C. Diabetes and hypertension. What is new? *Minerva Cardioangiol*. 2009; 57: 705-722.

3. Lawes CM, Vander Hoorn S, Rodgers A, International Society of Hypertension. Global burden of blood pressure-related disease, 2001. *Lancet*. 2008; 371: 1513-1518. doi: 10.1016/S0140-6736(08)60655-8

4. Grau M, Elosua R, Cabrera de Leon A, et al. Cardiovascular risk

factors in spain in the first decades of the 21st Century, a pooled analysis with individual data from 11 population-based studies:the DARIOS study. *Rev Esp Cardiol.* 2011; 64: 295-304. doi: 10.1016/j.recesp.2010.11.005

5. Wilo S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care.* 2004; 27: 1047-1053. doi: 10.2337/diacare.27.5.1047

6. Sowers JR, Epstein M, Frohlich ED. Diabetes, Hypertension and Cardiovascular disease. *Hypertension.* 2001; 37: 1053-1059. doi: 10.1161/01.hyp.37.4.1053

7. Matheus AS, Tannus LR, Cobas RA, Palma CC, Negrao CA, Gomes MB. Impact of diabetes on cardiovascular disease: An update. *Int J Hypertens.* 2013; 2013: 653789. doi: 10.1155/2013/653789

8. Patel BM, Mehta AA. Choice of antihypertensive agents in diabetic subjects. *Diab Vasc Res.* 2013; 10: 385-396. doi: 10.1177/1479164113485250

9. Graede P, Vedel P, Larsen N, Jensen HV, Parving HH, Pederson O. Multifactorial intervention and cardiovascular disease in patients. *N Engl J Med.* 2003; 348: 383-393. doi: 10.1056/NEJMoa021778

10. Kaur KK. Current management of obesity in an infertile female-recent advances and future prospective drugs. *J Pharm Nutr Sci.* 2013; 3: 1-13. doi: 10.6000/1927-5951.2013.03.03.2

11. Kaur KK, Allahbadia G, Singh M. An update on a etiopathogenesis and management of obesity. *Obes Control Ther.* 2016; 3(1): 1-17. doi: 10.15226/2374-8354/3/1/00123

12. Kaur KK, Allahbadia G, Singh M. Existing and prospective pathways for intervention in treatment of obesity in a novel way-a review. *MOJ Drug Des Develop Ther.* 2018; 2(3): 95-105. doi: 10.15406/mojddt.2018.02.00035

13. Kaur KK, Allahbadia G, Singh M. An update on bariatric surgery with long term efficacy and its utilization for medical therapy development from the different mechanism of action and other shortcomes to be outcome. *BAOJ Surgery.* 2018; 4: 2.

14. Kaur KK, Allahbadia G, Singh M. Hypothalamic inflammation and glioses as aetiopathogenetic factor in high fat diet induced obesity and various therapeutic options to resolve it. *Obes Res Open J.* 2017; 4(2): 44-60. doi: 10.17140/OROJ-4-132

15. Kaur KK, Allahbadia G, Singh M. Importance of simultaneous treatment of obesity and diabetes mellitus: A sequelae to the understanding of diabesity-A review. *Obes Res Open J.* 2019; 6(1): 1-10. doi: 10.17140/OROJ-6-136

16. Kaur KK, Allahbadia G, Singh M. Monoterpenes-a class of terpenoid group of natural products as a source of natural antidiabetic agents in the future -A Review. *CPQ Nutrition.* 2019; 3(4): 1-21.

17. Kaur KK, Allahbadia G, Singh M. Role of empagliflozin/metformin in patients with cardiovascular and combination therapy with SGLT2 inhibitor with metformin as initial treatment for type2 diabetes-advantages of oral fixed drug pill like renal risk-a short communication. *Archives of Diabetes and Endocrine System.* 2019; 2(1): 15-19.

18. Kaur KK, Allahbadia G, Singh M. Role of natural products in the treatment of diabesity with mechanism of action-a small communication. *Acta Scientific Nutritional Health.* 2019; 3: 140-142.

19. Kaur KK, Allahbadia G, Singh M. Sarcopenic obesity-a minireview-does it lead to a greater incident of type 2 diabetes, metabolic syndrome or mortality than when sarcopenia or obesity exist separately. *Archives of Diabetes and Endocrine System.* 2019; 2(1): 26-32.

20. Lastra G, Syed S, Kurukulasuriya LR, Manrique C, Sowers JR. Type 2 diabetes mellitus and hypertension: An update. *Endocrinol Metab Clin North Am.* 2014; 43: 103-122. doi: 10.1016/j.ecl.2013.09.005

21. Bolivar G. Essential Hypertension:an approach to its etiology and neurogenic pathophysiology. *Int J Hypertens.* 2013; 2013: 547809. doi: 10.1155/2013/547809

22. Sowers JR. Diabetes mellitus and vascular disease. *Hypertension.* 2013; 61: 943-947. doi: 10.1161/HYPERTENSIONAHA.111.00612

23. Cooper SA, Whalley-Connell A, Habibi J, et al. Renin-angiotensin–aldosterone system and oxidative stress on cardiovascular insulin resistance. *Am J Physiol Regul Integr Comp Physiol.* 2007; 293: H2009-23. doi: 10.1152/ajpheart.00522.2007

24. Maricia O, Grassi G. The autonomic nervous system and hypertension. *Circ Res.* 2014; 114: 1804-1814. doi: 10.1161/CIRCRESAHA.114.302524

25. Hirooka Y, Kimura Y, Nozoe M, Sagara Y, Ito K,Sunhgawa K. Amlodipine induced reduction of oxidative stress in the brain is associated with sympatho-inhibitory effect in stroke prone spontaneously hypertensive rats. *Hypertens Res.* 2006; 29: 49-56. doi: 10.1291/hypres.29.49

26. Kimura Y, Hirooka Y, Sagara Y, Sunagawa K. Long acting calcium channel blocker, azalnipidipine, increases endothelial nitric oxide synthase in the brain and inhibits sympathic nerve activity. *Clin Exp Hypertens.* 2007; 29: 13-21. doi: 10.1080/10641960601096745

27. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes mellitus (UKPDS 36) prospectivre observational study. *BMJ.* 2000; 321: 412-419. doi: 10.1136/bmj.321.7258.412

28. Volpe M, Battisoni A, Savoia C, Tocci G. Understanding and treating hypertension in diabetic populations. *Cardiovasc Diagn Ther.* 2015; 5: 353-363. doi: 10.3978/j.issn.2223-3652.2015.06.02

29. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010; 362: 1575-1585. doi: 10.1056/NEJMoa1001286

30. Arguedas JA, Loiva V, Wright JM. Blood pressure targets for hypertension in people with diabetes mellitus. *Cochrane Database Syst Rev.* 2013; 10: CD008277. doi: 10.1002/14651858.CD008277.pub2

31. Maricia G, Fagard R, Narkiewicz K, et al.2013.ESH/ESC 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). *J Hypertens.* 2013; 31: 1281-1357. doi: 10.1097/01.hjh.0000431740.32696.cc

32. James PA, Oparti S, Carter BL, et al. 2014.Evidence based guidelines for the management of high blood pressure in adults: Report from the panel members appointed to the Eigth Joint National Committeee (JNC 8). *JAMA.* 2014; 311: 507-520. doi: 10.1001/jama.2013.284427

33. Barrios V, Escobar C, Alonsa-Moreno FI, et al. Evolution of clinical profile ,treatment and blood pressure control in treated hypertensive patients according to the sex from 2002 to 2010 in Spain. *J Hypertens.* 2015; 33: 1098-1107. doi: 10.1097/HJH.0000000000000502

34. Hao G, Wang Z, Guo R, et al. Effects of ACEi/ARB in hypertensive patients with type 2 diabetes mellitus: A meta-analysis of randomized controlled studies. *BMC Cardiovasc Disord.* 2014; 14: 148. doi: 10.1186/1471-2261-14-148

35. Vejakama P, Thakkinstian A, Lerttrattanon D, Insathit A, Ngarmukos C, Attia I. Renoprotective effects of Renin-angiotensin – aldosterone system blockade in type 2 diabetic patients:a systematic review and network meta-analysis. *Diabetologia.* 2012; 55: 566-578. doi: 10.1007/s00125-011-2398-8

36. Parving HH, Brenner BM, McMurray JV, et al. Cardiorenal endpoints in a trial of aliskiren for type 2 diabetes. *N Engl J Med.* 2012; 367: 2204-2213. doi: 10.1056/NEJMoa1208799

37. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high risk patients. *N Engl J Med.* 2008; 359: 2417-2428. doi: 10.1056/NEJMoa0806182

38. Weber MA, Bakris GL, Jamerson K, et al. Cardiovascular events during hypertension therapies in patients with diabetes. *J Am Coll Cardiol.* 2010; 56: 77-85. doi: 10.1016/j.jacc.2010.02.046

39. Brenner BM, Cooper ME, De Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes mellitus and nephropathy. *N Engl J Med.* 2001; 345: 861-869. doi: 10.1056/NEJMoa011161

40. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non insulin dependent diabetes and Hypertension. *N Engl J Med.* 1998; 338: 645-652. doi: 10.1056/NEJM199803053381003

41. Tatti P, Pahor M, Byington RP, et al.Outcome results of the Fosinopril versus Amlodipine Cardiovascular events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care.* 1998; 21: 597-603. doi: 10.2337/diacare.21.4.597

42. Beri T, Hunsicker LG, Lewis JB, et al. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial of patients with type 2 diabetes mellitus and overt nephropathy. *Ann Intern Med.* 2003; 138: 542-549. doi: 10.7326/0003-4819-138-7-200304010-00010

43. Ostergren J, Poulter NR, Sever PS, et al. The Anglo-Scandinavian Cardiac Outcomes Trial: Blood pressure-lowering limb: Effects in patients with type II diabetes mellitus. *J Hypertens.* 2008; 26: 2103-2111. doi: 10.1097/HJH.0b013e328310e0d9

44. Gojanovic B, Felhl F, Liaudet L, Waeber B. Concomitant calcium entry blockade and inhibition of the Renin-angiotensin –system: A rationale and effective means for treating hypertension. *J ReninAngiotensin Aldosterone Syst.* 2008; 9: 1-9. doi: 10.3317/jraas.2008.007

45. Rizos CV, Elisaf M. Anti hypertensive drugs and glucose metabolism. *World J Cardiol.* 2014; 6: 517-530. doi: 10.4330/wjc.v6.i7.517

46. Scheen AJ. Renin-angiotensin–system inhibition prevents type 2 diabetes mellitus. Part 1. A meta-analysis of randomized clinical trials. *Diabetes Metab.* 2004; 30: 487-496. doi: 10.1016/s1262-3636(07)70146-5

47. Geng DF, Jin DM, Wu W, Liang YD, Wang JF. Angiotensin converting enzyme inhibitors for prevention of new onset type 2 diabetes mellitus: A meta-analysis of 72,128 patients. *Int J Cardiol.* 2013; 167: 2605-2610. doi: 10.1016/j.ijcard.2012.06.125

48. Geng DF, Jin DM, Wu W, Xu Y, Wang JF. Angiotensin receptor blockers for prevention of new onset type 2 diabetes mellitus: A Meta-analysis of 59,862 patients. *Int J Cardiol.* 2012; 155: 236-242. doi: 10.1016/j.ijcard.2010.10.011

49. Noto H, Goto A, Tsujimoto T, Nooa M. Effect of calcium channel blockers on incidence of diabetes: A Meta-analysis. *Diabetes Metab Syndr Obes.* 2013; 6: 257-261. doi: 10.2147/DMSO.S49767

50. Yang Y, Wei RB, Xing Y, et al. A Meta-analysis of the effects of angiotensin receptor blockers and calcium channel blockers on blood pressure, glycaemia and the HOMA-IR index in non diabetic patients. *Metabolism.* 2013; 62: 1858-1866. doi: 10.1016/j.metabol.2013.08.008

51. Fukao k, Shimada K, Hiki M, Kiyanagi T, Hirose K, et al. Effects of calcium channel blockers on glucose tolerance, re-analysis of data from the NAVIGATOR Study. *BMJ.* 2013; 347: 16745.

52. Buset Rios N, Rodriguez Esparragon F, Fernandez-Andrade Rodriquez C, Rodriquez Perez JC. Vascular and metabolic properties of manidipine. *Nefrologia.* 2011; 31: 268-274. doi: 10.3265/Nefrologia.pre2010.Nov.10643

53. Buset Rios N ,Rodriguez Esparragon F, Rodriquez Perez J. Cardiometabolic properties of manidipine beyong lowering arterial pressure? *Nefrologia.* 2009; 29(3): 203-207. doi: 10.3265/Nefrologia.2009.29.3.5078.en.full

54. Bangalore S, Parkar S, Grossman E, Messerli FH. A Meta-analysis of 94,492 patients with Hypertension treated with beta blockers to determine the risk of new onset diabetes mellitus. *Am J Cardiol.* 2007; 100: 1254-1262. doi: 10.1016/j.amjcard.2007.05.057

55. Agabitiflosei E, Rizzoni D. Metabolic profile of nevibiolol, a beta-adrenoceptor antagonist with unique characteristics. *Drugs.* 2007; 67: 1097-1107. doi: 10.2165/00003495-200767080-00001

56. Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvediolol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A Randomized Controlled Trial.*JAMA.* 2004; 292: 2227-2236. doi: 10.1001/jama.292.18.2227

57. Elliott WI, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: A network Meta-analysis. *Lancet.* 2007; 369: 201-207. doi: 10.1016/S0140-6736(07)60108-1

58. Barrios V, Escobar C. Which thiazide to choose as add on therapy for hypertension? *Integr Blood Press Control.* 2014; 7: 35-47. doi: 10.2147/IBPC.S40248

59. Stears AJ, Woods SJ, Watts MM, et al. A double blind ,placebo controlled ,cross over trial comparing the effects of amiloride and hydrochlorthiazide on glucose tolerance test in patients with essential hypertension. *Hypertension.* 2012; 59: 934-942. doi: 10.1161/HYPERTENSIONAHA.111.189381

60. Preiss D, Von Veldhuisen DJ, Sattar N, et al. Eplenorone and new onset diabetes in patients with mild heart failure:results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure [EMPHASIS-HF]. *Eur J Heart Fail.* 2012; 14: 909-915. doi: 10.1093/eurjhf/hfs067

61. Moreira MC, Pinto IS, Mourao AA, et al. Does the sympathetic nervous system contribute to the pathophysiology of metabolic syndrome? *Front Physiol.* 2015; 6: 234. doi: 10.3389/fphys.2015.00234

62. Fogari R. Ankle oedema and sympathetic activation. *Drugs.* 2005; 65: 21-27. doi: 10.2165/00003495-200565002-00004

63. Martinez-Martin FJ, Salz-Satjes M. Add on manidipine versus amlodipine in diabetic patients with Hypertension and microalbuminurea: The AMANDHA Study. *Expert Rev Cardiovasc Ther.* 2008; 6: 1347-1355. doi: 10.1586/14779072.6.10.1347

64. Martinez Martin FJ. Manidipine in hypertensive patients with metabolic syndrome: The MARIMBA Study. *Expert Rev Cardiovasc Ther.* 2009; 7: 863-869. doi: 10.1586/erc.09.53

65. Limura O, Shimamoto K. Efficacy and mode of action of manidipine: A new calcium antagonist. *Am Heart J.* 1993; 125(2Pt2): 635-642. doi: 10.1016/0002-8703(93)90215-u

66. Del Vechio L, Pozzi M, Salvetti A, et al. Efficacy and tolerability of manidipine in the treatment of hypertension in patients with non diabetic kidney disease without glomerular disease. Prospective, randomized double blind of parallel groups in comparison with enalapril. *J Nephrol.* 2004; 17: 261-269.

67. Fogari R, Mugellini A, Zoppi A, et al. Effect of successful hypertension control by manidipine or lisinopril on albuminurea and left ventricular mass in diabetic hypertensive patients with microalbuminurea. *Eur J Clin Pharmacol.* 2005; 61: 483-490. doi: 10.1007/s00228-005-0961-2

68. Fogari R, Malamani G, Zoppi A, et al. Effect on development of ankle oedema by adding delapril to manidipine in patients with mild to moderate essential hypertension: A threeway cross over study. *Clin Ther.* 2007; 29: 413-418. doi: 10.1016/s0149-2918(07)80079-8

69. Fogari R, Corradi l, Zoppi A, et al. Addition of manidipine improves the antiprotective effect of candedsartan in hypertensive patients with type II diabetes and microalbuminurea. *Am J Hypertens.* 2007; 20: 1092-1096. doi: 10.1016/j.amjhyper.2007.05.012

70. Richy FF, Laurent S. Efficacy and safety profiles of manidipine compared with amlodipine: A Meta-analysis of head to head trials. *Blood Press.* 2011; 20: 54-59. doi: 10.3109/08037051.2010.518670

71. Martell-Claros N, De la Cruz JJ. Manidipine for hypertension not controlled by dual therapy in patients with diabetes mellitus, a noncomparative, open-label study. *Clin Drug Investig.* 2011; 31(6): 427-434. doi: 10.2165/11587400-000000000-00000

72. Bakris GL, Serafidis PA,Weir MA, et al. Renal outcomes with different fixed dose combination therapies in patients with hypertension at high risk of cardiovascular events (ACCOMPLISH): A prespecified secondary analysis of randomized controlled trials. *Lancet.* 2010; 375:1173-1181. doi: 10.1016/S0140-6736(09)62100-0

73. Salz-Satjes M, Martinez-Martin FJ, Roca-Cusachs A. Factors associated with the reduction of albumin excretion in diabetic hypertensive patients: Differential effects of manidipine versus amlodipine. *Future Cardiol.* 2017; 13: 143-151. doi: 10.2217/fca-2016-0046

74. Salz-Satjes M, Martinez-Martin FJ. Treatment of hypertensive patients with diabetes: Beyond blood pressure control and focus on manidipine. *Future Cardiol.* 2016; 12: 435-447. doi: 10.2217/fca-2016-0027

75. Hayashi K, Wakino S, Sugano N, Ozawa Y, Homma K, Saruta T. Ca2+channel subtypes and pharmacology in the kidney. *Circ Res.* 2007; 100: 342-353. doi: 10.1161/01.RES.0000256155.31133.49

76. Ott C, Schneider MP, Raff U, et al. Effects of manidipine vs amlodipine on intrarenal haemodynamics in patients with arterial Hypertension. *Br J Clin Pharmacol*. 2013; 75: 129-135. doi: 10.1111/j.1365-2125.2012.04336.x

77. Nakami T, Martinez MF. Manidipine prevents hepatic C Reactive protein production and reactive oxygen species generation by down regulation of the age receptor expression, dependent on PPAR–gamma activation. *J Hypertens*. 2007; 25: S119-S120.

78. Kohlmann O Jr, Ribeiro AB. Estudio Brasileiro com Manidipina. Manidipine in the Treatment of stage I-II essential hypertension patients with overweight or android obesity. A Brazilian multicenter study of the efficacy, tolerability and metabolic effects. *Arq Bras Cardiol*. 2001; 77: 463-470.

79. Allue RC, Brotons FM. Efficacy and safety of manidipine in patients with hypertension aged 70 years or older. *Aging Health*. 2011; 7: 521-528. doi: 10.2217/ahe.11.35

80. Suzuki S, Ohtomo M, Satoh Y, et al. Effects of manidipine and delapril on insulin sensitivity in type 2 diabetic patients with essential hypertension. *Diabetes Res Clin Pract*. 1996; 33: 43-51. doi: 10.1016/0168-8227(96)01273-9

81. Martinez-Martin FJ, Macias-Batista A, Comi-Diaz C, Rodriquez-Rosas H, Soriano-Pererea P, Pedrianes-Martin P. Effects of manidipine and its combination with an ACE Inhibitor on insulin sensitivity and inflammatory and prothrombotic markers in Hypertensive patients with metabolic syndrome: The MARCADOR Study. *Clin Drug Investig*. 2011; 31: 201-212. doi: 10.2165/11587590-000000000-00000

82. Fogari R, Derosa G, Zoppi A, et al. Effects of manidipine/delapril versus olmesartan/hydrochlorothiazide combination therapy with type 2 diabetes mellitus. *Hypertens Res*. 2008; 3: 43-50. doi: 10.1291/hypres.31.43

83. Fogari R, Derosa G, Zoppi A, et al. Effects of manidipine/delapril versus olmesartan/hydrochlorothiazide combination on insulin sensitivity and fibrinogen in obese hypertensive patients.*Intern Med*. 2008; 47: 361-366. doi: 10.2169/internalmedicine.47.0449

84. Kohlmann O Jr, Roca Cusachs A, Laurent S, Schmieder RE,Wenzel RR, Fogari R. Fixed dose manidipine/delapril versus losartan/hydrochlorothiazide in hypertensive patients with type 2 diabetes mellitus and microalbuminurea. *Adv Ther*. 2009; 26: 313-324. doi: 10.1007/s12325-009-0015-8

85. Priess D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive lowdose compared with moderate dose statin therapy: A meta-analysis. *JAMA*. 2011; 305: 2556-2564. doi: 10.1001/jama.2011.860

86. Liberopoulos EN, Moutzouri E, Rizos CV, Barkas F, Liamis G, Elisaf MS. Effects of manidipine plus rosuvastatin on markers of insulin resistance in patients with impaired fasting glucose, hypertension and mixed dyslipidemia. *J Cardiovasc Pharmacol Ther*. 2013; 18: 113-118. doi: 10.1177/1074248412463611

87. Fogari R, Zoppi A, Corradi l, Preti P, Malamani GD, Mugellini A. Effects of different dihydropyridine calcium antagonists on plasma norepinephrine in essential hypertension. *J Hypertens*. 2000; 18: 1871-1875. doi: 10.1097/00004872-200018120-00023

88. Mugellini A, Preti P, Zoppi A, et al. Effects of manidipine/delapril combination vs irbesartan-hydrochlorothiazide combination in fibrinolytic function in Hypertensive patients with type II diabetes mellitus. *J Hum Hypertens*. 2004; 18: 687-691. doi: 10.1038/sj.jhh.1001726

89. Rossoni G, Manfredi B, Civelli M, Berti F, Razzetti R. Combined simvastatin with manidipine protects against ischemia-reperfusion injury in isolated hearts from normocholesterolemic rats. *Eur J Pharmacol*. 2008; 587: 224-230. doi: 10.1016/j.ejphar.2008.03.026

90. Galceran J, Plana J, Felip A, Pou G, Vila J, Soberino J. Manidipine treatment in patients with albuminurea not sufficiently reduced with renin-angiotensin–aldosterone system inhibitors. *Expert Rev Cardiovasc Ther*. 2010; 8: 751-757. doi: 10.1586/erc.10.48

91. Bohm M, Schumacher H,Teo KK, et al. Cardiovascular outcomes and achieved blood pressure in patients with and without diabetes at high cardiovascular risk. *Eur Heart J*. 2019; 40(25): 2032-2043.

92. American Diabetes Association. Cardiovascular disease and risk management (sec.9) in standards of medical care in Diabetes-2017. *Diabetes Care*. 2017; 40(Suppl1): S75-S87. doi: 10.2337/dc17-S012

93. Brunstrom M, Eliasson M, Nilsson PM, Carlberg B. Blood pressure treatment levels and choice of anti hypertensive agents in people with type 2 diabetes- an overview of systematic reviews. *J Hypertens*. 2017; 35: 453-462. doi: 10.1097/HJH.0000000000001183

94. Remonti LR, Dias S, Leitao CB, Kramer CK, Kiassman LP, etal.Classes of antihypertensive agents and mortality in hypertensive patients with type 2 diabetes- network meta-analysis of randomized trials. *J Diabetes Complications*. 2016;30:1192-200. doi: 10.1016/j.jdiacomp.2016.04.020

95. Montanari A, Lazzeroni D, Pela G, et al. Calcium channel blockade blunts the renal effects of acute nitric oxide synthase inhibition in healthy humans. *Am J Physiol Renal Physiol*. 2017; 312: F870-F878. doi: 10.1152/ajprenal.00568.2016

96. Gupta R, Sharma KK, Lodha S, et al. Quality of hypertension management in type 2 diabetes in India: A multisite prescription audit. *J Assoc Physicians India*. 2018; 66(9): 20-25.

97. Kaur KK, Allahbadia G, Singh M. Advantage of Cardiovascular Outcome Trials (CVOT's) for SGLT2 (Sodium Glucose Transporter 2) inhibitors in Type 2 Diabetes Mellitus (T2 DM). *EC Endocrinology and Metabolic Research*. 2019; 4(9): 38-44.

98. Schernthaner G, Karasik A, Abraitene A, et al. Evidence from routine clinical practice: EMPRISE provides a new perspective on CVOTs. *Cardiovasc Diabetol.* 2019; 18: 115. doi: 10.1186/s12933-019-0920-3

99. Huang CY, Ma T, Tien L, et al. A retrospective longitudinal study of anti hypertensive drug use and new–onset diabetes in Taiwanese patients. *Biomed Res Int.* 2013; 2013: 287696. doi: 10.1155/2013/287696

100. Chukwuma CI, Matsabisa MG, Ibrahim MA, Erukainure OL, Chablala MH, Islam MS. Medicinal plants with concomitant anti-diabetic and anti hypertensive effects as potential sources of dual acting therapies against diabetes and hypertension: A review. *J Ethnopharmacol.* 2019; 235: 329-360. doi: 10.1016/j.jep.2019.02.024

101. Chandra KS, Ramesh G. The fourth-generation Calcium channel blocker: Cilnidipine. *Indian Heart J.* 2013; 65(6): 691-695. doi: 10.1016/j.ihj.2013.11.001

102. Singh VK, Mishra A, Gupta KK, Misra R, Patel ML, Shilpa. Reduction of microalbuminuria in type-2 diabetes mellitus with angiotensin-converting enzyme inhibitor alone and with cilnidipine. *Indian J Nephrol.* 2015; 25(6): 334-339. doi: 10.4103/0971-4065.151764

103. Tanaka M, Sekioka R, Nishimura T, Ichihara A, Itoh H. Effects of cilnidipine on sympathetic nerve activity and cardiorenal function in hypertensive patients with type 2 diabetes mellitus: Association with BNP and aldosterone levels. *Diabetes Res Clin Pract.* 2014; 106(3): 504-510. doi: 10.1016/j.diabres.2014.09.056