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REVIEW

# Manidipine: an antihypertensive drug with positive effects on metabolic parameters and adrenergic tone in patients with diabetes

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## Abstract

Antihypertensive treatment of patients with diabetes should include those drugs with a positive effect on metabolic parameters. Most patients with diabetes require at least two antihypertensive agents. Combining a dihydropyridine calcium channel blocker with a renin-angiotensin-aldosterone system inhibitor is a rational approach. However, not all dihydropyridines are equal with respect to their effects on metabolic parameters. Thus, manidipine exerts a positive effect on insulin resistance. However, this effect has not been observed with amlodipine. On the other hand, the excessive activation of sympathetic nervous system has been related with an increase of insulin resistance, pulse pressure, and ankle edema rates. Compared with amlodipine, manidipine activates sympathetic nervous system to a lesser extent. As a result, treatment with manidipine represents a good option in hypertensive patients with diabetes.

**Keywords:** amlodipine, antihypertensive drug, calcium channel blocker, diabetes, hypertension, insulin resistance, manidipine, sympathetic nervous system.

## Citation

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# Diabetes and hypertension

## Importance of hypertension in patients with diabetes

Hypertension and diabetes are two leading causes of cardiovascular disease. Thus, diabetes is associated with a two- to three-fold increase in the risk of ischemic heart disease in men and a greater increase in women [1,2]. On the other hand, recent data have reported that about 54% of stroke, 47% of coronary heart disease, and nearly 14% of deaths worldwide are associated with arterial hypertension [3]. Both conditions are currently very common. In a pooled analysis with individual data from 11 studies in which 28,887 individuals aged 35–74 years were included, the prevalence of hypertension was 47% in men and 39% in women, whereas the prevalence of diabetes was 16% and 11%, respectively [4]. However, due to the aging of the population and that sedentary life style and obesity are continuously increasing, it is very likely that these figures will rise in the following years. Thus, whereas 171 million subjects had diabetes by the year 2000 worldwide, it has been calculated that these figures will grow to 350 million people by 2030 [5].

There is a close relationship between hypertension and diabetes. In fact, the presence of diabetes almost doubles the probability of exhibiting hypertension, and on the contrary, those patients with hypertension have a 2.5-fold increased risk of developing diabetes [6]. As a result, more than 60% of patients with diabetes had hypertension and when microalbuminuria is also present, the prevalence of hypertension reaches 90% of patients [6]. In addition, in patients with diabetes, about three quarters of cardiovascular outcomes are related with hypertension [1,7]. The concomitance of both conditions dramatically increases the risk of developing cardiovascular complications, particularly coronary heart disease [8]. Therefore, achieving the recommended risk factors' control targets has been shown to be the best option to reduce the overall cardiovascular risk in patients with type 2 diabetes [9].

## Diabetes and hypertension: etiopathogenic mechanisms

A number of different mechanisms have been proposed to explain the relationship between diabetes and hypertension and that justify the high risk of cardiovascular complications that these patients have [1,2,10]. Thus, the excessive activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, the oxidative stress, the low-grade inflammation status, the altered insulin-mediated vasodilatation, the impaired innate and adaptive immunity, the abnormal sodium processing by the kidney and the presence of nephropathy have been involved in the development of both hypertension and diabetes [10]. Although all these mechanisms may have a relevant impact on the homeostasis of every patient with hypertension and type 2 diabetes, the intensity in which each of these factors occur in a particular patient may vary between individuals [10–12]. In addition, obesity and increased visceral adiposity play also a key role in the pathogenesis of hypertension and diabetes. Thus, the chronic low-grade inflammation and the oxidative stress in the adipose tissue observed in obese patients promote the activation of the renin-angiotensin-aldosterone system [10–13]. Moreover, in patients with obesity, leptin, an adipokine produced in the adipose tissue, is increased and promotes sympathetic system activation [10].

Insulin resistance that is present in about a half of hypertensive patients, produces vascular damage, including abnormal function, vascular stiffness, hypertrophy, fibrosis and remodeling. In addition, insulin resistance enhances sympathetic output and promotes sodium reabsorption in the diluting segment of the distal nephron, leading to a decrease in sodium excretion and finally to an increase of blood pressure (BP) levels. Moreover, insulin resistance also promotes the activation of the renin-angiotensin-aldosterone system. Hyperinsulinemia causes volume and sodium retention in the kidney and activates sympathetic nervous system [2,10,12,14–16]. On the other hand, increased oxidative stress secondary to the excessive production of reactive oxygen species facilitates the development of insulin resistance, diabetes and hypertension [10,14].

Sympathetic nervous system activation is observed in patients with essential hypertension and diabetes. Although a number of factors have been involved in this activation, such as genetic influences, excessive salt intake or sedentary lifestyle, obesity is one of the most relevant factors. Obesity promotes sympathetic nervous system activation through various mechanisms, including the high-sodium-intake-related mechanisms, cardiopulmonary reflex dysfunction, renin-angiotensin-aldosterone system activation, central factors, baroreflex dysfunction, chemoreceptor dysfunction, insulin/leptin alterations or reactive oxygen species/nitric oxide imbalance. Remarkably, it has been reported that this abnormal balance may be partially corrected by chronic administration of some long-acting dihydropyridine calcium channel blockers [11,17–21].

Other mechanisms such as enhanced platelet aggregation and the presence of an abnormal balance between coagulation and fibrinolysis that promotes a procoagulant state have also been described in patients with hypertension and diabetes [2,10,11].

## Antihypertensive approach in patients with type 2 diabetes and hypertension

The UKPDS study showed in patients with type 2 diabetes that for each 10 mmHg decrease in systolic BP, the risk for any complication related to diabetes was reduced by 12% ($p<0.0001$), for deaths related to diabetes by 15% ($p<0.0001$), for myocardial infarction by 11% ($p<0.0001$), and for microvascular complications by 13% ($p<0.0001$). Remarkably, regarding the prevention of cardiovascular events, the beneficial effect of reducing BP was greater than that of glycemic control [22].

Whereas observational studies had suggested "the lower, the better" for BP in diabetes, randomized clinical trials have only demonstrated beneficial effects on macrovascular and microvascular complications when reducing BP levels to <140/90 mmHg. Even more, in some high-risk hypertensive patients with diabetes, excessive reduction of BP could be harmful [23]. For example, in ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, in which 4733 patients with type 2 diabetes were randomized to a systolic BP goal <120 mmHg (intensive therapy) or <140 mmHg (standard therapy), the risk for the primary composite outcome was similar between both groups after a mean follow-up of 4.7 years. However, intensive therapy was associated with a significant lesser risk of stroke (HR 0.59; 95% CI 0.39–0.89), but with a higher risk of serious adverse events attributed to antihypertensive treatment [24]. In other study that analyzed the results of five clinical trials, achieving higher reductions of BP (128/76 *vs* 135/83 mmHg) in patients with diabetes was associated with a trend towards a lower total mortality risk (RR 0.73; 95% CI 0.53–1.01) [25]. As a result, BP targets have been recently reconsidered for patients with diabetes and hypertension [23]. Thus, while previous guidelines suggested a BP target less than 130/80 mmHg for patients with diabetes, current guidelines have moved these recommendations to less than 140/85 mmHg (European Society of Hypertension/European Society of Cardiology) or <140/90 mmHg (Eighth Joint National Committee and American Society of Hypertension/International Society of Hypertension) [26–28]. On the other hand, different epidemiological studies have shown that although in the last years BP control rates have improved, the fact is that a great number of patients with hypertension and diabetes do not currently attain BP goals [29,30].

Although all first-line antihypertensive agents reduce BP to a similar extent, and in this context, all of them could be used in hypertensive patients with diabetes, the fact is that renin-angiotensin-aldosterone system inhibitors have been shown

to provide additional beneficial effects on cardiovascular and renal outcomes beyond BP control in this population [26–28]. A meta-analysis of 10 randomized controlled studies, with a total of 21,871 hypertensive patients with type 2 diabetes, that analyzed the effects of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) on cardiovascular events showed that the overall treatment with ACEi/ARBs significantly reduced the risk of cardiovascular events by 10% and the risk of cardiovascular mortality by 17% [31].

In addition, treatment with ACEi/ARB has been shown to be of particularly benefit to prevent or at least delay the development of nephropathy in patients with type 2 diabetes. Thus, in a meta-analysis of 28 studies (18 studies compared ACEi/ARB *vs* active drugs, 31 comparisons and 13 studies compared ACEi/ARB *vs* placebo, 20 comparisons), in comparison with other antihypertensive drugs, despite similar BP reductions, treatment with ACEi/ARB was associated with significant decreases in the risk of serum creatinine doubling and macroalbuminuria. Moreover, the proportion of patients who exhibited albuminuria regression was higher in those patients treated with ACEi/ARBs. In addition, there was a trend for a lower risk of end-stage renal disease and microalbuminuria in the ACEi/ARB group [32]. However, although the use of ACEi or ARB is of particular benefit in this population, different clinical trials have demonstrated that the combination of both, ACEi and ARB should be avoided, since no beneficial effect has been observed, but a higher risk of adverse events [33,34]. Therefore, unless contraindicated, every patient with hypertension and type 2 diabetes should be treated with an ACEi or an ARB [26–28].

However, it has been reported that up to 75% of patients with diabetes and hypertension will require at least two antihypertensive drugs to achieve BP goals [29,30,35]. Traditionally, in most cases, initial combined therapy has included a renin-angiotensin-aldosterone system inhibitor plus a thiazide-like diuretic or a calcium channel blocker. However, the ACCOMPLISH (Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension) trial showed in 11,506 patients high-risk hypertensive patients that the combination of an ACEi plus a dihydropyridine calcium channel blocker reduced the risk for cardiovascular events to a higher extent when compared to the combination of the same ACEi plus hydrochlorothiazide [36]. These results were confirmed in the subgroup of patients with diabetes. Thus, in the subgroup of patients with diabetes, compared with the hydrochlorothiazide group, the combination with the calcium channel blocker reduced the risk of cardiovascular death, myocardial infarction, stroke, hospitalization for angina, resuscitated arrest and coronary revascularization by 21% (HR 0.79; 95% CI 0.68–0.92, $p$=0.003). Of note, coronary events and revascularizations were also less common in those patients treated with the combination of the ACEi plus the dihydropyridine calcium channel blocker [37].

As a result, when combined therapy is required for the treatment of a patient with hypertension and type 2 diabetes, it seems that the combination of a renin-angiotensin–aldosterone-system inhibitor plus a dihydropyridine calcium channel blocker should be preferred.

## Role of calcium channel blockers in the treatment of patients with hypertension and diabetes

Overall, calcium channel blockers effectively reduce BP levels with a good tolerability profile. They are widely used in hypertensive patients with diabetes. For example, in RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) study, in which 1513 patients with type 2 diabetes and nephropathy were randomized to receive losartan or placebo in addition to conventional antihypertensive treatment, around 80% of patients in both groups received calcium channel blockers to achieve BP goals [38].

A number of studies have analyzed the effects of calcium channel blockers on cardiovascular outcomes in patients with hypertension and diabetes. In ABCD (Appropriate Blood Pressure Control in Diabetes) study, compared with enalapril, treatment with nisoldipine was associated with a significant higher incidence of fatal and nonfatal myocardial infarction among those patients with non-insulin-dependent diabetes and hypertension [39]. In FACET (Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial) study, despite BP was reduced to a similar extent and no differences were found in total serum cholesterol, HDL cholesterol, HbA1c, fasting serum glucose or plasma insulin between groups, patients randomized to fosinopril had a significantly lower risk of major vascular events compared with the patients randomized to amlodipine in patients with hypertension and non-insulin-dependent diabetes [40]. By contrast, in IDNT (Irbesartan Diabetic Nephropathy Trial), in which 1715 adults with type 2 diabetic nephropathy and hypertension were randomized to receive irbesartan, amlodipine or placebo in addition to conventional antihypertensive treatment, time to cardiovascular death, myocardial infarction, congestive heart failure, strokes and coronary revascularization similarly occurred in the three groups. However, patients receiving amlodipine had a significantly lower rate of myocardial infarction when compared with placebo (HR 0.58; 95% CI 0.37–0.92; $p$ = 0.02) [41]. In the large subgroup of patients with diabetes ($n$ = 5,137) included in the BP-lowering arm of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) study, the amlodipine-based treatment (perindopril could be added as required) was associated with a reduction in the incidence of the composite endpoint of total cardiovascular events and procedures compared with the atenolol-based regimen (thiazide could be added as required) (HR 0.86; 95% CI 0.76–0.98; $p$=0.026). In addition, the amlodipine-based treatment was associated with a reduction of fatal and nonfatal strokes,

peripheral arterial disease and noncoronary revascularization procedures [42].

All these data indicate that although renin-angiotensin-aldosterone system inhibitors should be considered the first-line therapy for the treatment of patients with diabetes and hypertension, when a second antihypertensive drug is required to achieve BP goals, a calcium channel blocker should be considered. This is not surprising, since the combination of a dihydropyridine calcium channel blocker with a renin-angiotensin-aldosterone system inhibitor has been shown to have complementary mechanisms of action that strength their efficacy, with a low incidence of side effects [2,43,44].

## Importance of metabolic control in patients with diabetes and hypertension

The best approach to reduce overall cardiovascular risk in patients with diabetes is the comprehensive treatment of all cardiovascular risk factors. However, some antihypertensive drugs may promote unfavorable effects on metabolic parameters and excepting when a compelling indication exists, they should be avoided, particularly in patients with diabetes or at risk of developing diabetes, such as those patients with metabolic syndrome. By contrast, those antihypertensive drugs that exhibit neutral or favorable metabolic effects should preferably be used in this population [2,45].

Many studies have reported that renin-angiotensin-aldosterone system inhibitors exhibit beneficial effects on glucose homeostasis. Thus, in a meta-analysis that analyzed the effects of renin-angiotensin–aldosterone-system inhibition on the incidence of new-onset diabetes, 10 randomized clinical trials (8 concerning hypertensive population and 2 concerning heart failure patients) were included. Whereas 7.4% of patients receiving ACEi or ARBs developed new-onset diabetes mellitus, this occurred in 9.63% of patients in the control group (relative risk reduction 22%; 95% CI 18–26%; $p<0.00001$). This beneficial effect was similar regardless the type of renin-angiotensin-aldosterone system inhibitor used (ACEi or ARB), the type of comparator (placebo or beta-blockers/diuretics or amlodipine) or the type of the underlying condition (hypertension or heart failure) [46]. Recent meta-analyses have shown that ACEi reduce the risk of new-onset diabetes compared with beta-blockers/diuretics by 22%, with placebo by 21% and with calcium channel blockers by 15% [47]. The same authors found in other meta-analysis that ARBs decrease the risk of new-onset diabetes compared with beta-blockers/diuretics by 27%, with placebo by 17% and with calcium channel blockers by 24% [48]. These data are not surprising, since renin-angiotensin-aldosterone system plays a key role in the pathogenesis of both hypertension and glucose metabolism [45].

Overall, calcium channel blockers have a neutral effect on glucose metabolism. Thus, in a meta-analysis of 10 randomized clinical trials including 108,118 hypertensive patients with no pre-existing diabetes, calcium channel blockers were associated with a higher incidence of diabetes than ACEIs or ARB, but with a lower incidence compared with beta-blockers or diuretics [49]. Other meta-analyses have outlined similar results [50,51]. However, not all calcium channel blockers have the same effect on glucose homeostasis. For example, small studies have suggested that azelnidipine could ameliorate insulin resistance [52]. However, the results obtained with manidipine regarding its beneficial effects on insulin resistance are more consistent [53–56].

By contrast, overall, diuretics and beta-blockers have been associated with unfavorable effects on glucose homeostasis [45]. In fact, different studies have shown that treatment with beta-blockers is associated with a greater risk for the development of diabetes. In a meta-analysis of 94,492 patients with hypertension treated with beta-blockers, treatment with beta-blockers increased the risk for new-onset diabetes mellitus by 22% (RR 1.22; 95% CI 1.12–1.33) compared with nondiuretic antihypertensive drugs. Remarkably, the risk for diabetes was greater with atenolol [57]. However, not all beta-blockers have the same effect on glucose metabolism. Thus, a number of studies have shown that some beta-blockers such as bisoprolol, carvedilol or nebivolol may not be harmful for glucose homeostasis [58–60].

Globally, diuretics increase the risk for new-onset diabetes. Thus, in a meta-analysis that identified 48 randomized groups of 22 clinical trials with 143,153 participants who did not have diabetes at randomization, the association of antihypertensive drugs with incident diabetes was lowest for ARB and ACEi followed by calcium channel blockers and placebo, beta-blockers and diuretics in rank order [61]. However, as with beta-blockers, not all diuretics have the same effect on glucose homeostasis. Thus, it seems that chlorthalidone may have a more favorable metabolic profile compared with other thiazide or thiazide-like diuretics [45,62]. In addition, other study showed that whereas amiloride and hydrochlorothiazide reduced BP levels to a similar extent, treatment with hydrochlorothiazide was associated with an increase of glucose levels after a 2-hour oral glucose tolerance test, but not with amiloride [63]. Finally, the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study was aimed to investigate the effect of eplerenone in addition to conventional therapy on clinical outcomes in 2737 patients with systolic heart failure and mild symptoms. In those patients without diabetes at baseline ($n$=1,846), eplerenone did not increase the risk of new-onset diabetes (HR 0.94, 95% CI 0.59–1.52) [64].

## Adrenergic tone and arterial hypertension

The sympathetic nervous system plays a pivotal role in the pathophysiology of both hypertension and metabolic control. Chronic hyperactivity of the sympathetic nervous system has been shown to promote the development of obesity, hyperglycemia, insulin resistance and hypertension [11,17,18,65]. Moreover, an excessive sympathetic activation system may

increase pulse pressure. This is very relevant, since high pulse pressure has been associated with a worse cardiovascular prognosis [66]. In addition, sympathetic overactivation after arterial vasodilation increases the risk of developing ankle edema. As a result, those calcium channel antagonists that activate the sympathetic nervous system to a lesser extent will have a better tolerability profile, with a lesser risk of ankle edema [67].

The first generation of dihydropyridine calcium channel blockers was characterized by instantaneous release, short lifetime and quick absorption. Consequently, tachycardia and sympathetic activation were common. By contrast, last generation of dihydropyridines, characterized by a long lifetime and prolonged action, activate sympathetic nervous system to a lesser extent. As a result, the latter drugs have better cardiovascular and tolerability profile [55,56]. Despite that, not all third generation of dihydropyridine calcium channel blockers have the same effect on sympathetic activity [68,69].

# Manidipine: beneficial effects beyond blood pressure control

## Efficacy and safety of manidipine

Manidipine is a third generation dihydropyridine calcium channel blocker that effectively reduces BP levels with a sustained effect over 24 hours, without a significant increase of heart rate or cardiac output [70]. Different studies have analyzed the antihypertensive efficacy of manidipine [68,69,71–82]. These studies have shown that manidipine reduces BP levels to a similar extent than enalapril, lisinopril or amlodipine, among other antihypertensive drugs. Thus, in a study performed in patients with type 2 diabetes and hypertension, after 24 weeks of treatment, manidipine 10 mg and enalapril 10 mg daily similarly reduced BP levels (–23/–13 mmHg and –20/–12 mmHg, respectively; $p<0.01$ *vs* baseline; $p$=NS between groups) [75]. The MAISH study was a European randomized, double-blind, multicenter and parallel-group study in which 195 patients aged ≥60 years old with isolated systolic hypertension received manidipine 10–20 mg once daily or amlodipine 5–10 mg once daily. Chlortalidone 25 mg once daily could be added if BP remained uncontrolled despite treatment with the high dose of manidipine or amlodipine. After 12 weeks of treatment, similar reductions of systolic BP were observed in both groups (–19.5 and –18.4 mmHg, respectively; $p$=NS) [79]. In a meta-analysis that included 4 head-to-head randomized and controlled clinical trials of at least 12 months of treatment comparing the antihypertensive efficacy and safety of manidipine 20 mg with that of amlodipine 10 mg, a total of 838 patients were analyzed (436 in the manidipine group and 402 in the amlodipine group). The antihypertensive efficacy of both drugs was similar (effect size for diastolic BP=–0.08 and for systolic BP=–0.01 ($p$=NS for both systolic and diastolic BP) [81].

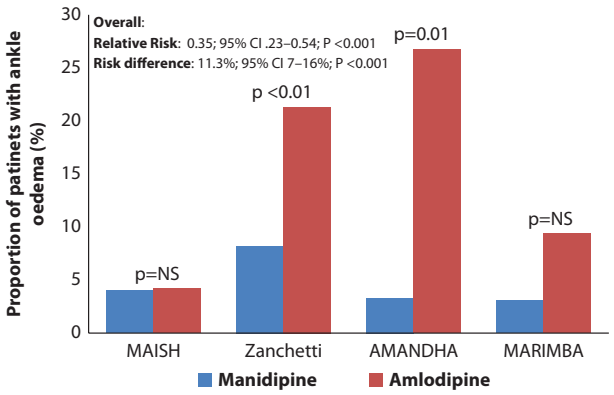
All these data show that manidipine is effective as monotherapy. However, different studies have demonstrated that manidipine can also be used as add-on therapy, particularly to renin-angiotensin-aldosterone system inhibitors. Thus, in a noncomparative and open-label study in which 136 patients with type 2 diabetes and uncontrolled BP despite a combination of a low-dose diuretic plus an ACEi or an ARB, the addition of manidipine10–20 mg/daily reduced BP values by approximately –22/–9 mmHg ($p<0.001$) after 6 months of treatment [82].

Microalbuminuria is a common complication of patients with hypertension and diabetes. This is very important, since microalbuminuria is associated with an increased cardiovascular risk [26]. Although reducing BP to recommended targets is mandatory to reduce urinary albumin excretion rates, some antihypertensive drugs have exhibited additional beneficial effects beyond BP control. In this context, ACEi or ARB, but not both simultaneously, are the drugs of choice in the treatment of patients with diabetes and hypertension, particularly when microalbuminuria is present [26–28]. The ACCOMPLISH trial showed that compared with the combination of benazepril plus hydrochlorothiazide, the initial antihypertensive treatment with benazepril plus amlodipine slowed progression of nephropathy to a greater extent [83]. This is in accordance with a study performed in a hypertensive population with diabetes, microalbuminuria and uncontrolled BP despite treatment with candesartan, in which compared with the addition of hydrochlorothiazide 12.5 mg daily, the addition of manidipine 10 mg daily reduced urinary albumin excretion to a higher extent, despite BP was similarly reduced [78].

However, not all calcium channel blockers offer the same renal protection. In fact, different studies have shown in hypertensive patients with or without diabetes that manidipine exhibits a higher renal protection when compared with amlodipine, despite similar BP reduction, alone or in combination with a renin-angiotensin-aldosterone system inhibitor [68,69]. Thus, in a multivariate analysis of the AMANDHA study, the assigned treatment (manidipine *vs* amlodipine) was independently associated with changes in urinary albumin excretion [84]. These differences may be explained by the fact that amlodipine block only L-type calcium channels, whereas manidipine blocks L- and T-type calcium channels. L-type receptors are only present in the afferent arterioles but not in the efferent arterioles. As a result, when blocking L-type calcium channels, vasodilation is limited to afferent arterioles. This causes glomerular hypertension and, secondarily, an increase in urinary albumin excretion. By contrast, T-type calcium channels are present in both the afferent and the efferent arterioles. Therefore, the blockade of these receptors vasodilates both arterioles, leading to a decrease of intraglomerular pressure and, consequently, to a reduction of urinary albumin excretion rates [68,85–87].

Ankle edema is the most relevant side effect associated with the treatment of dihydropyridines. Ankle edema associated

**Figure 1. Risk of ankle edema with manidipine and amlodipine.**




CI: confidence interval.
Data taken from [68,69,73,79,81].

with dihydropyridine calcium channel blockers occurs because of an increase in intracapillary pressure due to the selective increase in the postcapillary tone secondarily to the sympathetic activation [68]. Since not all calcium channel blockers have the same effect on sympathetic system activation, the risk of ankle edema may be different between dihydropyridines. In fact, a number of studies have demonstrated that despite a similar effect on BP reduction, the rates of ankle edema are significantly higher with amlodipine than with manidipine. Thus, in the meta-analysis of Richy FF and Laurent S, compared with amlodipine, treatment with manidipine was associated with a 65% lesser risk of developing ankle edema (relative risk 0.35; 95% CI .23–0.54; risk difference 11.3%; 95% CI 7–16%) (Figure 1) [81]. Moreover, since renin-angiotensin-aldosterone system inhibitors dilate the arterial vascular bed and venous capacitance vessels, leading to a reduction of intracapillary pressure, the addition of a renin-angiotensin-aldosterone system inhibitor to the treatment with dihydropyridine calcium channel blockers may reduce the ankle edema associated with dihydropyridines [43,68]. Thus, in a study that enrolled patients with previously untreated hypertension, the addition of delapril to manidipine partially counteracted the microcirculatory changes induced by manidipine responsible for ankle edema. In fact, in this three-way crossover study, ankle edema was clinically evident in three patients after receiving manidipine in monotherapy, but only in one patient with the combination of manidipine and delapril [77].

## Effects of manidipine on metabolic parameters

Different studies have shown that manidipine exerts positive effects on metabolic parameters in hypertensive population. It has been suggested that manidipine increases insulin sensitivity by stimulating the formation and the differentiation of adipocytes as well as preserving PPAR-γ activity [54–56,88].

These beneficial metabolic effects have been shown with manidipine in monotherapy but also when combined with renin-angiotensin-aldosterone system inhibitors.

In an open-label and noncomparative study performed in 102 stage I–II essential hypertensive patients of both sexes with overweight or central obesity, the metabolic effects of manidipine 10 to 20 mg once daily for 12 weeks were analyzed. No significant changes in metabolic parameters (fasting plasma glucose, total, HDL- and LDL-cholesterol, triglycerides and insulin sensitivity index) were reported (Table 1) [89]. In other study performed in patients with hypertension aged 70 years or older, treatment with manidipine during 6 months was not associated with alterations in glucose or lipid profiles, although there was a trend to a reduction of triglycerides levels (Table 1) [90].

In an open trial performed in Japanese non-insulin-dependent diabetes mellitus patients with essential hypertension, treatment with either manidipine or delapril for 3 months improved the insulin sensitivity index as well as the glucose-effectiveness. In addition, there were no differences between plasma glucose, serum total triglycerides, and cholesterol or lipoprotein cholesterol fractions and body weight between groups (Table 1) [91]. In a multicenter and double-blind trial comparing the efficacy and safety of manidipine and enalapril in patients with type 2 diabetes and hypertension for 24 weeks, significant reductions in HbA1c (from 6.7% to 6.2%) and blood glucose concentrations (from 152 to 143 mg/dL) were observed only in the manidipine group ($p<0.05$). No significant changes were observed in other metabolic parameters (Table 1) [75].

In the MARCADOR study, the effects of manidipine and its combination with an ACEi on insulin sensitivity and metabolic, inflammatory and prothrombotic markers were analyzed. In this study with a PROBE design, 120 patients aged 35–75 years with stage I–II essential hypertension and metabolic syndrome were randomized to receive amlodipine 10 mg, telmisartan 80 mg, manidipine 20 mg or manidipine 10 mg/lisinopril 10 mg. After 14 weeks of treatment, compared with amlodipine, manidipine had significantly superior effects on insulin resistance (–26.5 *vs* –3.0%), LDL-cholesterol (–6.8 *vs* +1.7%) and other metabolic parameters. Whereas manidipine was associated with a slightly higher increase in insulin sensitivity than manidipine/lisinopril, combined therapy was significantly more effective than manidipine and telmisartan for improving other metabolic parameters (Table 1, Figure 2) [92]. In the MARIMBA study, 64 subjects without diabetes but with metabolic syndrome, including impaired fasting glucose (>5.6 mmol/l) and hypertension, were randomized to receive manidipine 20 mg or amlodipine 10 mg for 12 weeks. Despite BP was similarly reduced by both treatments, plasma adiponectin (which are inversely associated with the development of insulin resistance and metabolic syndrome) was increased (32.9%; $p=0.011$) and plasma TNF-alpha was reduced by manidipine (–37.1%; $p=0.019$), but neither was significantly changed by amlodipine. In addition, the HOMA insulin resistance index was

**Table 1. Effects of manidipine on metabolic parameters.**

| Study | Population | Duration of treatment | Effects on metabolic parameters | Effects on other parameters |
|---|---|---|---|---|
| Kohlmann and Ribeiro [89] | Stage I–II essential hypertensive patients with overweight or central obesity | 12 weeks | • Fasting plasma glucose: $p$=NS.<br>• Lipid profile: $p$=NS.<br>• Insulin sensitivity index. $p$=NS. | • Blood pressure was reduced from 159±15/102±5 mmHg to 141±15/90±8 mmHg.<br>• Tolerability was very high. |
| Cristófol Allué and Manzanares Brotons [90] | Patients with hypertension ≥70 years | 6 months | • Glucose profile: $p$=NS.<br>• Lipid profile: $p$=NS (there was a trend to a reduction of triglycerides levels). | • Blood pressure was reduced from 163.3±12.7/88.8±9.6 mmHg to 147.8±10.0/80.3±6.4 mmHg ($p$<0.01).<br>• Microalbuminuria was reduced from 27.1 to 8.3% during the study ($p$=0.004).<br>• Tolerability was good. |
| Suzuki et al. [91] | Non-insulin-dependent diabetes mellitus patients with essential hypertension | 3 months | • Manidipine improved the insulin sensitivity index from 3.35±0.61 ($\times 10^{-4}$ $min^{-1}$ $microU^{-1}$ $ml^{-1}$) to 4.70±1.34 ($p$<0.05).<br>• Manidipine improved the glucose-effectiveness from 1.60±0.64 ($\times 10^{-2}$ min) to 2.19±0.38 ($p$<0.05).<br>• There were no differences between plasma glucose, serum total triglycerides, and cholesterol or lipoprotein cholesterol fractions, heart rate and body weight after 3 months on manidipine | • Treatment with manidipine significantly reduced systolic and diastolic blood pressures. |
| Luque Otero et al. [75] | Patients with type 2 diabetes and hypertension | 24 weeks | • Manidipine significantly reduced HbA1c (from 6.7% to 6.2%; $p$<0.05.<br>• Manidipine significantly reduced blood glucose concentrations from 152 to 143 mg/dL; $p$ <0.05). | • Blood pressure was significantly reduced by manidipine (from 164±12/97.5±5 mmHg to 141±12/84.5±6 mmHg; $p$ <0.01).<br>• Manidipine was well tolerated |
| Martinez-Martin et al. [92] | Patients aged 35–75 years with stage I–II essential hypertension and metabolic syndrome | 14 weeks | • Compared with amlodipine, manidipine had significantly superior effects on:<br>◦ Insulin resistance (–26.5 *vs* –3.0%).<br>◦ Albumin/creatinine ratio (–28.2 *vs* –3.6%).<br>◦ Low-density lipoprotein cholesterol (–6.8 *vs* +1.7%). | • Both treatments significantly reduced blood pressure from baseline.<br>• Amlodipine was associated with a significantly greater incidence of adverse effects compared with manidipine (26.7 *vs* 3.3%). |

*(Continued)*

**Table 1.** (*Continued*)

| Study | Population | Duration of treatment | Effects on metabolic parameters | Effects on other parameters |
|---|---|---|---|---|
| Martínez Martín [69] | Subjects without diabetes but with metabolic syndrome | 12 weeks | • Manidipine significantly increased plasma adiponectin (32.9%; $p$=0.011).<br>• Manidipine significantly decreased plasma TNF-alpha (–37.1%; $p$=0.019).<br>• Manidipine significantly reduced the HOMA insulin resistance index (–21.3%; $p$=0.007). | • Manidipine and amlodipine significantly reduced blood pressure from baseline.<br>• Albuminuria was significantly reduced by manidipine (–37.3%; $p$=0.003) but not by amlodipine.<br>• Manidipine was better tolerated than amlodipine. |
| Martínez Martín and Sáiz-Satjés [68] | Patients with diabetes and uncontrolled hypertension and microalbuminuria despite full-dose treatment with a renin-angiotensin-aldosterone system inhibitor | Initial phase: 6 months. Extension phase: 18 months. | • Insulinization rates and changes in insulin dose were less necessary with manidipine when compared with amlodipine. | • Manidipine and amlodipine similarly reduced blood pressure levels during the study.<br>• Urinary albumin excretion was reduced by 65.5% with manidipine *vs* 20% with amlodipine ($p$<0.01) at 6 months and 62.7 *vs* 16.6% ($p$<0.01) at the end of the extension phase.<br>• Manidipine was better tolerated than amlodipine. |
| Liberopoulos et al. [97] | Patients with mixed dyslipidemia, hypertension, and impaired fasting glucose | 3 months | • An increase in HOMA-insulin resistance index and fasting insulin levels was reported with olmesartan plus rosuvastatin, whereas no significant change was observed in the manidipine plus rosuvastatin group.<br>• Fasting plasma glucose and HbA1c did not change significantly in any group. | |

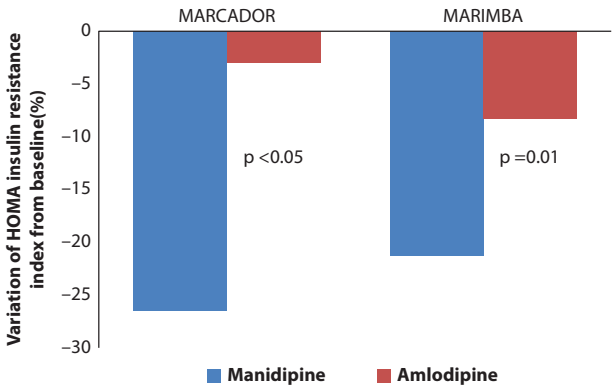
Data taken from [68,69,75,89-92,97].

significantly reduced by manidipine (–21.3%; $p$=0.007) but not by amlodipine (–8.3%; $p$=0.062) (Table 1, Figure 2) [69].

In the AMANDHA study, the efficacy and safety of adding manidipine 20 mg *vs* amlodipine 10 mg to the treatment of patients with diabetes and uncontrolled hypertension and microalbuminuria despite full-dose treatment with a renin-angiotensin-aldosterone system inhibitor for at least 6 months were analyzed. BP was similarly reduced by both treatments [68]. In a post-hoc analysis, insulinization rates and changes in insulin dose during the study were analyzed. The use of oral antidiabetics and insulin was modified during the study according to local practice. Baseline HbA1c was 8.1±1.1% in the group of patients assigned to manidipine and 8.2±1.0% in those patients assigned to amlodipine. After 2 years of treatment, HbA1c was 7.6±1.3% and 7.9+0.9%, respectively ($p$=NS). At baseline, 72.1% of patients treated with manidipine and 73.3% of those treated with amlodipine were on insulin treatment. Among these patients, the doses of insulin were 0.47±0.13 U/kg and 0.44±0.16 U/Kg, respectively. After 2 years of treatment, the doses of insulin were 0.36±0.11 U/Kg and 0.51±0.17 U/Kg, respectively ($p_{manidipine\ vs\ baseline}$=0.031; $P_{manidipine\ vs\ amlodipine}$=0,012). In addition, among those patients not receiving insulin at baseline, 11.8% of patients assigned to manidipine and 50% of those subjects assigned to amlodipine started treatment with insulin during the study (relative risk reduction 76.4%; absolute risk reduction 38.2%; odds ratio 7.5) (Table 1).

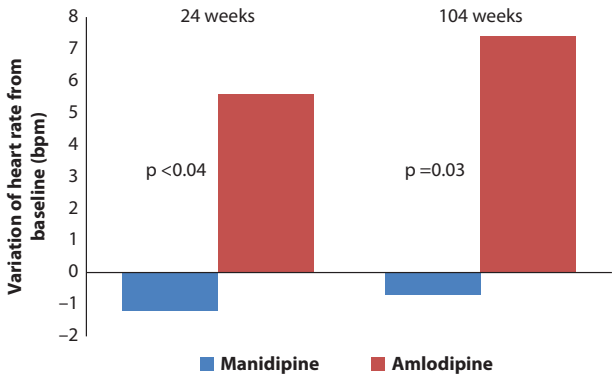
In a study that compared the effects of manidipine/delapril *vs* olmesartan/hydrochlorothiazide combination therapy in

**Figure 2. Effect of treatment with manidipine and amlodipine on HOMA insulin resistance index.**




Data taken from [69,92].

**Figure 3. Effect of treatment with manidipine and amlodipine on heart rate in the AMANDHA study.**




Data taken from [68].

elderly hypertensive patients with type 2 diabetes, 158 patients were randomized to receive combination treatment of 10 mg manidipine plus 30 mg delapril or 20 mg olmesartan plus 12.5 mg hydrochlorothiazide for 48 weeks. At study end, despite similar sitting BP reductions, whereas no changes in metabolic parameters were observed with manidipine/delapril, an increase in HbA1c (+0.7%; $p<0.05$), uric acid (+0.4 mg/dL; $p<0.05$), and triglycerides (+41.3 mg/dL; $p<0.05$), and a decrease in HDL-cholesterol (−3.4 mg/dL; $p<0.05$) were found in the olmesartan/hydrochlorothiazide group [93]. In other study performed in obese hypertensive patients, the delapril/manidipine combination but not the olmesartan/hydrochlorothiazide combination significantly decreased insulin resistance and plasma fibrinogen levels, despite similar BP lowering efficacy [94]. In another study performed in hypertensive patients with type 2 diabetes and microalbuminuria, whereas BP was reduced to a similar extent by both treatments after one year of follow-up, there was a trend for a reduction of blood glucose concentration from baseline with manidipine/delapril (mean change −0.2 mmol/L, $p=0.064$), but not with the losartan/hydrochlorothiazide combination [95].

Finally, it has been reported that potent statins have the potential to promote the development of diabetes [96]. In a study that compared the effect of manidipine 20 mg plus rosuvastatin 10 mg with that of olmesartan 20 mg plus rosuvastatin 10 mg on markers of insulin resistance in patients with mixed dyslipidemia, hypertension and impaired fasting glucose, after 3 months of treatment, a significant increase in HOMA-IR index by 14% (from 2.4 to 2.7; $p=0.02$ *vs* baseline) was reported with olmesartan plus rosuvastatin, whereas no significant change was observed in the manidipine plus rosuvastatin group (1.7 to 1.7; $p$=NS *vs* baseline, $p=0.04$ *vs* olmesartan plus rosuvastatin group). In addition, an increase in fasting insulin levels was observed in the olmesartan plus rosuvastatin group (from 10.1 to 10.9 µU/mL; $p<0.05$ *vs* baseline), but not with manidipine plus rosuvastatin (from 7.3 to 7.5 µU/mL; $p$=NS *vs* baseline, $p=0.02$ *vs* olmesartan plus rosuvastatin). No significant changes in fasting plasma glucose or glycosylated hemoglobin were observed in any group (Table 1). As a result, manidipine seems to ameliorate the possible statin-associated increase in insulin resistance as compared with olmesartan [97].

## Effects of manidipine on adrenergic tone

Due to their instantaneous release, short lifetime and quick absorption properties, first generation of dihydropyridine calcium channel blockers exhibited some adverse effects including sharp drops in BP, tachycardia and sympathetic activation. By contrast, third-generation calcium channel blockers have a long lifetime and prolonged action. As a result, effects on sympathetic activation are less marked with these drugs [55]. However, not all third-generation calcium channel blockers have the same effect on sympathetic activation.

In AMANDHA study, whereas heart rate increased by 5.6 and 7.4 bpm after 24 and 104 weeks of treatment with amlodipine, respectively ($p=0.011$ and $p=0.018$ *vs* baseline, respectively), no significant differences were found with manidipine (−1.2 and −0.7 bpm, respectively; $p$=NS *vs* baseline; $p=0.041$ at week 24 and $p=0.033$ at week 104 *vs* amlodipine) (Figure 3). These results were in accordance with the changes reported in urinary metanephrine and normetanephrine excretion rates at week 24. In fact, whereas urinary metanephrine and normetanephrine levels increased in the amlodipine group, no significant changes were observed in the manidipine group. In addition, significant correlations were found between both metanephrine and normetanephrine excretion rates and pulse pressure, as well as with heart rate (Table 2) [68]. In other study performed in patients with hypertension and type 2 diabetes mellitus, in which manidipine and enalapril were compared, neither drug affected heart rate values (Table 2) [75]. Similarly, in a study performed in stage I–II hypertensive population,

**Table 2. Effects of manidipine on adrenergic tone.**

| Study | Population | Duration of treatment | Effects on adrenergic tone | Effects on other parameters |
|---|---|---|---|---|
| Martínez Martín and Sáiz-Satjés [68] | Patients with diabetes and uncontrolled hypertension and microalbuminuria despite full-dose treatment with a renin-angiotensin-aldosterone system inhibitor | Initial phase: 6 months.<br>Extension phase: 18 months. | • Whereas heart rate significantly increased with amlodipine during the study, no significant differences were found with manidipine.<br>• These results were in accordance with the changes reported in urinary metanephrine and normetanephrine excretion rates at week 24. | • Manidipine and amlodipine similarly reduced blood pressure levels during the study.<br>• Urinary albumin excretion was reduced by 65.5% with manidipine *vs* 20% with amlodipine ($p<0.01$) at 6 months and 62.7 *vs* 16.6% ($p<0.01$) at the end of the extension phase.<br>• Manidipine was better tolerated than amlodipine. |
| Luque Otero et al. [75] | Patients with hypertension and type 2 diabetes mellitus | 24 weeks | • Neither manidipine nor enalapril modified heart rate values. | • Blood pressure was significantly reduced by manidipine (from 164±12/97.5±5 mm Hg to 141±12/84.5±6 mm Hg; $p<0.01$).<br>• Manidipine was well tolerated |
| Kohlmann and Ribeiro [89] | Stage I-II hypertensive patients with overweight or central obesity | 12 weeks | • Heart rate was not significantly modified by manidipine. | • Blood pressure was reduced from 159±15/102±5mmHg to 141±15/90±8mmHg.<br>• Tolerability was very good . |
| Fogari et al. [98] | Essential hypertensive patients | 24 weeks | • Significant increases in plasma norepinephrine levels were observed with amlodipine (+34.9%) and felodipine (39.4%) but not with lacidipine (+7.1%) and manidipine (+2.9%). | • All drugs similarly reduced clinic BP during the study. |

Data taken from [68,75,89,98].

heart rate was not significantly modified by manidipine (Table 2) [89].

Remarkably, in a study specifically designed to analyze the effects of different 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 hypertensive patients, significant increases in plasma norepinephrine levels were observed with amlodipine and felodipine (+34.9% and +39.4%, respectively; $p<0.01$ *vs* placebo) but not with lacidipine (+7.1%; $p$=NS) and manidipine (+2.9%, $p$=NS) (Table 2) [98].

On the other hand, in a study that compared the effects of delapril-manidipine and irbesartan-hydrochlorothiazide combinations on fibrinolytic function in hypertensive patients

with type II diabetes, whereas the combination delapril-manidipine improved the fibrinolytic function, the association irbesartan-hydrochlorothiazide worsened it [99]. The different activation of sympathetic nervous system promoted by chronic treatment with dihydropyridine calcium channel blockers together with their differential effects on fibrinolytic function could have an impact on cardiovascular outcomes. In fact, experimental data have demonstrated that simvastatin and manidipine interact positively in protecting the heart from ischemia-reperfusion injury [100].

Finally, since differences in sympathetic overactivation after arterial vasodilation have been shown to be related with differences in ankle edema rates, calcium channel blockers that activate the sympathetic nervous system to a lesser extent may exhibit a lesser risk of ankle edema [67]. This is the case of manidipine when compared with amlodipine, as previously commented [80].

# Discussion

Patients with diabetes and hypertension exhibit a very high cardiovascular risk [1–3]. The 2017 American Diabetes Association guidelines recommend a target of less than 140/90 mmHg for individuals with diabetes (level of recommendation A), but a target of less than 130/80 mmHg could be appropriate for some patients with diabetes at high risk of cardiovascular disease, if they can be achieved without undue treatment burden (level of recommendation C) [101]. Unfortunately, a great number of patients with diabetes and hypertension do not attain BP goals [29,30]. This is the consequence of the insufficient use of combined therapy [29,30]. In fact, the majority of hypertensive patients with diabetes will require at least two drugs to attain BP targets [29,30,35,102].

On the other hand, since a comprehensive approach is necessary to reduce cardiovascular risk in patients with diabetes [2,45], it would be appropriate to use preferentially in this population those antihypertensive drugs that have demonstrated a positive effect on metabolic parameters. In this context, the use of an ACEi or an ARB, but not both simultaneously, is unquestionable [26,101,103], and likely after the ACCOMPLISH trial, also the use of a dihydropyridine calcium channel blocker as add-on therapy when required [36,37].

However, not all dihydropyridine calcium channel blockers are equal with respect their effects on metabolic parameters. Whereas manidipine exerts a positive effect on insulin resistance, amlodipine does not. Thus, in the AMANDHA study, despite a similar BP reduction, insulinization rates and changes in insulin dose were less necessary with manidipine when compared with amlodipine [68]. In addition, it has been reported that manidipine exerts a positive effect on oxidative stress [104].

Even though third-generation dihydropyridine calcium channel blockers activate sympathetic nervous system to a lesser extent when compared with first-generation drugs [55], there are important differences between third-generation dihydropyridine calcium channel blockers. In the AMANDHA study, whereas heart rate increased by 7.4 bpm with amlodipine after 2 years of treatment, no significant differences were found with manidipine. This was directly related with changes in urinary metanephrine and normetanephrine excretion rates [68]. Since the excessive activation of sympathetic nervous system has been related with an increase of insulin resistance, pulse pressure and ankle edema rates [11,17,18,65,67], manidipine should be considered over other dihydropyridines in the treatment of hypertensive patients with diabetes, metabolic syndrome or at risk of developing diabetes. In addition, the lesser risk of ankle edema observed with manidipine could assure a better medication adherence. In fact, assuring an adequate medication adherence is mandatory in the management of patients with chronic conditions such as those with arterial hypertension or diabetes [105].

# Conclusions

Renin-angiotensin–aldosterone-system inhibitors are the treatment of choice of patients with diabetes and hypertension. But when a second antihypertensive drug is required, a calcium channel blocker should be chosen. In this context, manidipine seems a better option than amlodipine.

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