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TOPIC HIGHLIGHT

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# Antihypertensive drugs and glucose metabolism

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## Abstract

Hypertension plays a major role in the development and progression of micro- and macrovascular disease. Moreover, increased blood pressure often coexists with additional cardiovascular risk factors such as insulin resistance. As a result the need for a comprehensive management of hypertensive patients is critical. However, the various antihypertensive drug categories have different effects on glucose metabolism. Indeed, angiotensin receptor blockers as well as angiotensin converting enzyme inhibitors have been associated with beneficial effects on glucose homeostasis. Calcium channel blockers (CCBs) have an overall neutral effect on glucose metabolism. However, some members of the CCBs class such as azelnidipine and manidipine have been shown to have advantageous effects on glucose homeostasis. On the other hand, diuretics and β-blockers have an overall disadvantageous effect on glucose metabolism. Of note, carvedilol as well as nebivolol seem to differentiate themselves from the rest of the β-blockers class, being more attractive options regarding their effect on glucose homeostasis. The adverse effects of some blood pressure lowering drugs on glucose metabolism may, to an extent, compromise their cardiovascular protective role. As a result the effects on glucose homeostasis of the various blood pressure lowering drugs should be taken into account when selecting an antihypertensive treatment, especially in patients which are at high risk for developing diabetes.



**Key words:** Hypertension; Glucose metabolism; Antihypertensive drugs

**Core tip:** Hypertension is a major contributor to the development and progression of cardiovascular disease. Increased blood pressure often coexists with insulin resistance. The various antihypertensive drugs have different effect on glucose metabolism. Indeed, angiotensin receptor blockers as well as angiotensin converting enzyme inhibitors have been associated with beneficial effects on glucose homeostasis. Calcium channel blockers are considered to have neutral metabolic effects. On the other hand, diuretics and β-blockers have an overall disadvantageous effect on glucose metabolism. As a result the metabolic effects of the various blood pressure lowering drugs should be taken into account when selecting an antihypertensive treatment.

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## INTRODUCTION

Hypertension is a growing epidemic affecting an important percentage of the population[1]. Hypertensive patients have increased risk for the development and progression of both microvascular and macrovascular complications. As a result the need for a comprehensive management of high blood pressure is essential.

Hypertension is strongly associated with risk factors that impair glucose homeostasis and is often presented as a component of the metabolic syndrome. Indeed,

hypertension is related with obesity, insulin resistance as well as diabetes mellitus[2,3]. As a result, hypertensive patients have a 2.5-fold higher risk of type 2 diabetes mellitus (T2DM) onset compared with normotensive subjects[4]. The various classes of antihypertensive drugs have different effects on blood glucose metabolism. Indeed, antihypertensive agents, such as β-blockers and thiazide diuretics have been associated with negative effects on blood glucose in contrast to other classes, such as angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACE-I). As a result, the treatment of hypertensive subjects should be carefully selected as to not further deteriorate an already at risk glucose homeostasis.

## METHODS

We searched PubMed up to December 2013 using combinations of the following keywords: hypertension, glucose metabolism, glucose homeostasis, antihypertensive drugs, angiotensin converting enzyme inhibitors, ARBs, calcium channel blockers (CCB), β blockers, renin inhibitors, alpha blockers, diuretics. Major randomized controlled trials, original papers, review articles and case reports were included. The references of these articles were scrutinized for relevant articles. For articles not written in English, only the abstracts were considered. A minor limitation of this review is that our literature search was exclusively based on the PubMed database.

## RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

The renin angiotensin aldosterone system (RAAS) is strongly associated with glucose homeostasis. A number of studies have identified antihypertensive drugs that act by intervening in the RAAS as overall having beneficial effects on glucose metabolism.

### *Angiotensin converting enzyme inhibitors*

The majority of clinical trials evaluating the effects of ACE-I on glucose metabolism have showed a positive outcome. Large clinical trials have revealed that ACE-I are associated with a lower incidence of new-onset T2DM in hypertensive subjects. The heart outcomes prevention evaluation (HOPE) study demonstrated the favorable influence of ramipril on cardiovascular (CV) disease (CVD) incidence in high risk patients[5]. Patients recruited were ⩾ 55 years old, had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other CV risk factor [hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol (HDL-C) levels, cigarette smoking, or documented microalbuminuria]. For a mean period of 5 years the HOPE trial randomized the above high-risk patients ($n$ = 9279) to ramipril (10 mg/d) or placebo. Ramipril reduced new onset diabetes by 34% ($P$ < 0.001 *vs* placebo)[5]. However, there are some limitations of the HOPE results regarding new onset diabetes. Indeed, diabetes development in HOPE was not a pre-specified endpoint of the study. Moreover, the diagnosis of diabetes was patient reported.

Similarly, the Captopril Prevention Project (CAPPP) study was a prospective, randomized trial which compared the effect of captopril *vs* antihypertensive treatment with diuretics, β-blockers, or both in hypertensive patients ($n$ = 10985)[6]. Treatment with captopril was associated with fewer patients developing diabetes compared with the control group (OR = 0.79; 95%CI: 0.67-0.94; $P$ = 0.007). However, because of the design of the study, the query arises as to whether the differences in development of T2DM in the CAPPP trial were due to a protective effect of ACE-I or a deleterious effect of β-blockers and diuretics. Another limitation of the study was that blood pressure as well as diabetes mellitus at baseline was more common in the captopril group than in the group that received conventional treatment. In addition, in the captopril group a diuretic or a CCB was added to treatment in order to achieve the blood pressure goal.

The Antihypertensive and Lipid-Lowering Treatment to prevent heart attack trial (ALLHAT) was a randomized, double-blind, trial which evaluated whether treatment with a CCB or an ACE-I lowers the incidence of coronary heart disease (CHD) or other CVD events *vs* treatment with a diuretic[7]. Patients ($n$ = 33357) with hypertension and at least one other cardiac heart disease risk factor were randomized to chlorthalidone, amlodipine, or lisinopril for a mean follow-up of 4.9 years. Lisinopril treatment reduced the relative risk of developing T2DM by 30% (95%CI: 23%-37%; $P$ < 0.001) compared with patients treated with chlorthalidone and by 17% (95%CI: 7%-26%; $P$ < 0.01) compared with patients treated with the amlodipine[7].

The studies of left ventricular dysfunction (SOLVD) was a double-blind trial which randomized patients with asymptomatic left ventricular (LV) dysfunction to receive enalapril or placebo for a mean follow-up of 37.4 mo[8]. Enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations compared with placebo[8]. A retrospective study evaluated the effect of enalapril on the incidence of diabetes in patients from the SOLVD trial[9]. Enalapril significantly reduced the incidence of diabetes compared with placebo (HR = 0.22; 95%CI: 0.10-0.46; $P$ < 0.0001)[9].

On the other hand, some studies have shown that ACE-I have a neutral effect on glucose metabolism. A study in patients with T2DM and hypertension ($n$ = 24) resulted in no change in insulin sensitivity after trandolapril treatment[10]. Similarly, enalapril treatment did not affect insulin sensitivity in patients with essential hypertension ($n$ = 20)[11]. Moreover, lisinopril did not affect insulin sensitivity in healthy volunteers ($n$ = 22)[12]. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study evaluated the effects of ramipril or placebo in patients ($n$ = 5269) without CVD but with impaired fasting glucose levels or impaired glucose tolerance. Patients received ramipril (up to 15 mg

per day) or placebo (and rosiglitazone or placebo) for a median of 3 years[13]. Although ramipril treatment did not reduce the incidence of diabetes, it increased regression to normoglycemia in the study population ($P$ = 0.001). The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up (DREAM On) study followed patients from the DREAM trial for a median 1.6 years after the end of the trial[14]. Ramipril did not influence diabetes occurrence. Similarly, regression to normoglycemia was not altered by ramipril.

A meta-analysis of randomized control trials associated ACE-I treatment with a reduction of new-onset T2DM (RR = 0.73; 95%CI: 0.63-0.84)[15]. Similar were the results of another meta-analysis of randomized clinical trials where ACE-I had a smaller incidence of new-onset T2DM (OR = 0.77; 95%CI: 0.72-0.82; $P$ < 0.0006) compared with control groups[16].

### ARBs

Treatment with ARBs has also been associated with an overall beneficial effect on glucose homeostasis. Indeed, large clinical trials have associated ARB treatment with lower incidence of new-onset T2DM. The losartan intervention for endpoint reduction (LIFE) in hypertension study was a double-blinded, randomized, parallel-group trial in patients ($n$ = 9193) aged 55-80 years with essential hypertension (sitting blood pressure 160-200/95-115 mmHg) and LV hypertrophy[17]. Patients were randomized to losartan or atenolol based antihypertensive treatment for a mean follow-up of 4.8 years[17]. Losartan treatment was associated with a reduction of new-onset T2DM compared with the control group (HR = 0.75; 95%CI: 0.63-0.88; $P$ = 0.001).

The Antihypertensive treatment and Lipid Profile In a North of Sweden Efficacy Evaluation (ALPINE) study compared the effect of hydrochlorothiazide, alone or in combination with atenolol, against candesartan, alone or in combination with felodipine, in newly diagnosed patients with primary hypertension ($n$ = 342)[18]. After 12 mo, fasting plasma glucose and fasting serum insulin increased in the diuretic group, while a decrease was observed in the candesartan group ($P$ < 0.001 for the comparison of the 2 groups). The incidence of new-onset T2DM was higher in the hydrochlorothiazide (4.1%) group compared with the candesartan group (0.5%; $P$ = 0.03)[18].

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) was a prospective, double-blind, randomized trial that recruited hypertensive patients with additional CV risk factors[19]. Study subjects were randomized to either valsartan or amlodipine based regimen. Drug uptitration or the addition of further antihypertensive drugs, excluding ARBs, was allowed to achieve BP control. The valsartan based group had a smaller incidence of new-onset T2DM compared with the amlodipine group (HR = 0.77; 95%CI: 0.69-0.86; $P$ < 0.0001)[19].

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) study was a double-blind randomized control trial which evaluated candesartan *vs* placebo in patients with heart failure ($n$ = 7599) for a median follow-up of 37.7 mo[20]. Among patients without a history of diabetes, new-onset T2DM was significantly lower in the candesartan group compared with the placebo group (HR = 0.78; 95%CI: 0.64-0.96; $P$ = 0.020)[20]. The CHARM program consisted of 3 component trials, each comparing candesartan with placebo in a distinct population of patients with symptomatic heart failure: (1) the CHARM-Alternative which included patients with LV ejection fraction (LVEF) ⩽ 40% and intolerant of ACE-I; (2) the CHARM-Added which included patients with LVEF ⩽ 40% who were treated with an ACE-I; and (3) the CHARM-Preserved which included patients with LVEF > 40%. The candesartan group had a smaller incidence of T2DM compared with placebo only in the CHARM-Preserved trial (OR = 0.60; 95%CI: 0.41-0.86; $P$ = 0.005).

The nateglinide and valsartan in impaired glucose tolerance outcomes research (NAVIGATOR) was a double-blind, randomized clinical trial in subjects with impaired glucose tolerance with known CVD or with CV risk factors[21]. Patients ($n$ = 9518) were randomized to receive valsartan (up to 160 mg daily) or placebo for a median of 5.0 years. The valsartan group had a smaller incidence of T2DM compared with placebo (HR = 0.86; 95%CI: 0.80-0.92; $P$ < 0.001)[21]. Despite the reduction of T2DM incidence, valsartan treatment did not reduce the rate of CV events.

On the other hand, the Study on Cognition and Prognosis in the Elderly (SCOPE) evaluated the effects of candesartan vs placebo in elderly patients aged 70-89 years ($n$ = 4964) with hypertension for a mean follow-up of 3.7 years[22]. Open-label active antihypertensive therapy was added as needed. There was not a significant difference regarding new-onset T2DM between the 2 groups[22]. Similarly the CHARM-Added as well as the CHARM-Alternative studies did not show a difference regarding new-onset T2DM with candesartan treatment[20].

A number of meta-analyses indicate the protective role of ARB treatment regarding T2DM development. Geng *et al*[23] in a meta-analysis of 11 randomized control trials with 79773 patients (59862 non-diabetic patients at baseline) showed a beneficial effect of ARBs on T2DM development. Incidence of new-onset diabetes was significantly reduced in the ARBs group compared with controls (OR = 0.79; 95%CI: 0.74-0.84). This reduction of T2DM incidence was apparent in the comparison of ARBs to placebo (OR = 0.83; 95%CI: 0.78-0.89), β-blockers (OR = 0.73; 95%CI: 0.62-0.87), CCBs (OR = 0.76; 95%CI: 0.68-0.85) and non-ARBs (OR = 0.57; 95%CI: 0.36-0.91)[23]. ARBs were associated with significant reduction in the risk of new-onset diabetes in patients with hypertension (OR = 0.74; 95%CI: 0.68-0.81), heart failure (OR = 0.70; 95%CI: 0.50-0.96), impaired glucose tolerance (OR = 0.85; 95%CI: 0.78-0.92) or cardiocerebrovascular diseases (OR = 0.84; 95%CI: 0.72-0.97). A meta-analysis by Abuissa *et al*[15] of randomized controlled trials associated ARBs treatment with

a reduction of new-onset T2DM [RR = 0.77 (95%CI: 0.71-0.83)][15]. Another meta-analysis of randomized clinical trials showed that ARBs had a smaller risk of new-onset T2DM (OR = 0.79; 95%CI: 0.73-0.85; $P < 0.00001$) compared with control groups[16]. Similarly, Cheung et al in a meta-analysis of studies with ARBs showed that sartans were associated with a decrease of new-onset diabetes[24].

**Telmisartan:** Among members of the ARB family, some have the ability to partially activate PPARγ. Indeed, when various ARBs were evaluated regarding their PPARγ activating capacity, telmisartan was identified as the most prominent one[25,26]. Irbesartan was also associated with a milder activation of PPARγ. However only telmisartan retained its PPARγ-activating ability in lower concentrations usually attained during oral drug treatment[25]. This capacity of telmisartan can be attributed, at least partially, to its unique structure which differentiates it from other ARBs as well as to its structural resemblance with pioglitazone, a full PPARγ agonist[25]. Telmisartan in contrast to thiazolidinediones is only a partial PPARγ agonist. This leads to a diverse but overlapping gene expression compared with full activation of PPARγ and thus bestowing upon telmisartan unique pleiotropic effects[27].

A number of studies have identified telmisartan as having beneficial effects on glucose homeostasis both in non-diabetic subjects[28,29] as well as diabetic patients[30,31]. Furthermore, studies comparing telmisartan with other ARBs have shown that telmisartan had more favorable effects on glycemic profile[32,33]. Hypertension often coexists with dyslipidemia as commonly seen in metabolic syndrome. Moreover, there have been studies associating statin treatment with deteriorating effects on glucose metabolism[34-37]. Indeed, in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin trial (JUPITER)[38] rosuvastatin was associated with an increase in physician-reported newly diagnosed diabetes ($P = 0.01$) and an increase in glycated hemoglobin (HbA1c) *vs* placebo ($P = 0.001$). We have shown that telmisartan not only retains its beneficial effects on glucose homeo=stasis when co-administered with a statin, but also seems to negate any adverse effect of statin therapy on glycemic indices[39]. Patients ($n$ = 151) with mixed dyslipidemia, stage 1 hypertension and prediabetes were randomized to receive rosuvastatin (10 mg/d) plus telmisartan 80 mg/d or irbesartan 300 mg/d or olmesartan 20 mg/d[39]. After 6 mo, the homeostasis Model Assessment Insulin Resistance (HOMA-IR) index improved only in the telmisartan group (-29%) compared with either irbesartan (+16%; $P < 0.01$ *vs* RT) or olmesartan group (+14%; $P < 0.05$ *vs* RT) ($P < 0.05$ for all *vs* baseline).

A number of large clinical trials have evaluated the effect of telmisartan on the incidence of new-onset T2DM. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) evaluated the effects of telmisartan on hard clinical endpoints[40]. High risk patients ($n$ = 25620) with coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage were randomized to 3 groups and were followed for a median period of 56 mo. The first group received telmisartan (80 mg/d), the second group ramipril (10 mg/d) and the third group telmisartan plus ramipril (80/10 mg/d). The ONTARGET trial did not reveal any difference between ramipril (6.7%) and telmisartan (7.5%; HR = 1.12; 95%CI: 0.97-1.29) regarding new onset diabetes[40].

The Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with CVD (TRANSCEND) came as a complementary study to ONTARGET[41]. High risk patients ($n$ = 5926) intolerant to ACE-I with coronary, peripheral or cerebrovascular disease or diabetes with end-organ damage were randomized to telmisartan (80 mg/d) or placebo on top of any current therapy. TRANSCEND had the same primary endpoint as ONTARGET. A clear trend in reducing new clinical diagnosis of diabetes with telmisartan was seen in the TRANSCEND trial. The telmisartan group had lower new diabetes incidence (11%) *vs* placebo (12.8%; $P = 0.081$).

The prevention regimen for effectively avoiding second strokes (PRoFESS) study evaluated the effects of telmisartan on stroke incidence after a mean period of 30 mo[42]. Patients ($n$ = 20332) with a history of recent ischemic stroke were randomly assigned (2 × 2) to receive either both aspirin (25 mg/twice daily) and extended-release dipyridamole (200 mg/twice daily) or clopidogrel (75 mg/d); and telmisartan (80 mg/d) or placebo. Similarly, in the PRoFESS a trend was seen in reducing new onset diabetes with telmisartan (1.2%) *vs* placebo (1.5%; $P = 0.1$).

Although the TRANSCEND and PRoFESS both only showed trends for the reduction of new-onset T2DM, it should be noted that both of them had some limitations regarding their power to identify beneficial effects of telmisartan on diabetes onset. Indeed, more than one third of the TRANSCEND population had already a history of diabetes, thus decreasing the power of the remaining study population to detect any mild beneficial effect on T2DM development. Moreover, a great percentage (37%) of the PRoFESS population was already treated with ACE-Is, which have an established overall positive effect regarding new onset diabetes prevention[43]. Therefore, again any benefits of telmisartan would be harder to detect on-top of an ACE-I therapy. Moreover, the PRoFESS had a much smaller follow up period in contrast to studies with ARBs that showed benefits in new onset diabetes like the LIFE[17] and VALUE[19], Indeed, the PRoFESS population was monitored for 2.5 years *vs* 4.8 and 4.2 years for the LIFE and VALUE populations, respectively. This difference could explain why telmisartan showed only a trend for reduction of new onset diabetes.

### *Renin inhibitors*

Aliskiren is the first approved renin inhibitor which acts by directly inhibiting the renin enzyme at the point of

RAAS activation, blocking the conversion of angiotensinogen to angiotensin I and decreasing levels of angiotensin I and angiotensin Ⅱ[44]. A limited number of studies have evaluated the capacity of aliskiren to affect glucose metabolism. In a recent study, hypertensive patients with abnormal LV diastolic dysfunction but with normal LV systolic function ($n$ = 78) were randomized to aliskiren (up to 300 mg/d) treatment or control group which was treated with β-blockers or CCBs[45]. Fasting insulin and glucose remained unchanged in the aliskiren group, in contrast to the control group where an increase in both fasting insulin ($P$ = 0.03) and glucose ($P$ = 0.003) were observed. In another double-blind trial, patients with diabetes mellitus and hypertension ($n$ = 837) were randomized to once-daily aliskiren (150 mg titrated to 300 mg after four weeks), ramipril (5 mg titrated to 10 mg) or the combination for eight weeks[46]. No changes in HbA1c and fasting plasma glucose were observed in any treatment group. Another study randomized hypertensive patients with metabolic syndrome to aliskiren (300 mg/d) or losartan (100 mg/d)[47]. At study end patients performed an euglycemic hyperinsulinemic clamp and insulin sensitivity was assessed by glucose infusion rate. Insulin resistance improved only in the aliskiren group compared with losartan group ($P$ < 0.05 between groups).

### Mechanisms

The RAAS plays a major role both in the pathogenesis of hypertension as well as glucose homeostasis. As a result, a number of mechanisms have been suggested that can play a role in the overall beneficial effect that drugs which effect RAAS have on glucose metabolism.

Bradykinin may play an important role towards a beneficial effect on glucose homeostasis. The ACE beyond the conversion of angiotensin I to angiotensin Ⅱ can also decrease bradykinin levels[48]. Indeed, ACE promotes the degradation of bradykinin to inactive fragments *via* a kininase Ⅱ - mediated mechanism[49]. As a result, ACE-I can increase bradykinin levels[50]. Bradykinin has been shown to promote insulin sensitivity at the skeletal muscle level[51,52].

The principal glucose transporter protein that mediates insulin-stimulated glucose transport into muscle and adipose tissues is the glucose transporter type 4 (GLUT4), thus playing a key role in the regulation of glucose homeostasis[53]. Angiotensin Ⅱ decreases GLUT-4 translocation to the cell membrane[54,55]. As a result the RAAS inhibition could promote insulin sensitivity. Indeed, the inhibition of AT1 receptors prevented the decline of GLUT-4 in a diabetic rat heart model[56]. Moreover, both ACEIs and ARBs have been associated with increase of GLUT-4 protein expression in skeletal muscle and myocardium in insulin-resistant animal models[57].

Moreover, angiotensin Ⅱ inhibits adipogenic differentiation of human adipocytes *via* the AT1 receptor[58]. Angiotensin Ⅱ may inhibit preadipocytes recruitment, resulting in the storage of lipids in muscle and other tissues, thus increasing insulin resistance[59]. As a result, the blockade of RAAS would promote the recruitment of preadipocytes thereby increasing the number of small insulin-sensitive adipocytes leading to improved insulin sensitivity.

Furthermore, angiotensin Ⅱ can promote the production of inflammatory cytokines[60]. Inflammatory cytokines promote oxidative stress thus also leading to increased insulin resistance. In addition, endothelial dysfunction is also associated with insulin resistance[61]. Angiotensin converting enzyme inhibitors have also been shown to improve vascular function and insulin-mediated vascular responses[61]. Furthermore, ACE-I may also have direct beneficial effects on pancreatic β cells[62].

In addition ACE inhibition can lead to vasodilation of blood vessels[63]. This vasodilation has as a result the increment of total perfused area and thus increases glucose uptake and insulin sensitivity[64,65]. The activation of the sympathetic nervous system has also been associated with insulin resistance[66]. Both ACE-I[67] as well as ARBs[68] have been shown to decrease levels of catecholamines such as norepinephrine and epinephrine, thus further contributing to amelioration of insulin resistance.

Potassium levels play a significant role in insulin secretion since hypokalemia substantially impairs the insulin secretory response to glucose. As a result the increase of potassium levels by inhibiting the RAAS may also contribute to the improvement of glucose levels. Moreover, magnesium has also been shown to affect glucose homeostasis. Indeed, magnesium deficiency is associated with both a reduced cellular insulin action[69] and impaired insulin secretion[70]. The inhibition of the RAAS system leads to increased magnesium levels. A pooled analysis of studies using ACEIs in patients ($n$ = 96) with essential hypertension found that changes in insulin sensitivity index (ISI) were directly correlated to alterations in serum magnesium levels[71].

## CCBS

CCBs are generally considered as having an overall neutral metabolic profile. Indeed, a recent meta-analysis of 10 randomized clinical trials evaluated the effect of CCB treatment on new onset T2DM[72]. The overall risk of diabetes among subjects taking CCBs was not significant (RR = 0.99; 95%CI: 0.85-1.15). Compared with other classes of antihypertensive drugs, CCBs were associated with a higher incidence of diabetes than ACEIs (pooled risk ratio 1.23; 95%CI: 1.01-1.51) or ARBs (1.27; 95%CI: 1.14-1.42) and a lower incidence compared with β-blockers (RR = 0.83; 95%CI: 0.73-0.94) or diuretics (RR = 0.82; 95%CI: 0.69-0.98).

Another recent meta-analysis of 5 clinical trials compared the efficacy of ARBs and CCBs regarding their effect on insulin resistance as assessed using the HOMA-IR index in non-diabetic patients[73]. Both ARBs and CCBs had a similar effect on blood pressure reduction. However, ARBs reduced the HOMA-IR index (weighted mean difference -0.65, 95%CI: -0.93--0.38) and fasting plasma insulin (weighted mean difference -2.01, 95%CI:

-3.27--0.74) significantly more than CCBs. A recent re-analysis of data from the NAVIGATOR trial showed that CCBs were not associated with new onset diabetes (HR = 0.95; 95%CI: 0.79-1.13)[74].

Of note overdose of CCB has been associated with hyperglycemia primarily due to the blockade of pancreatic L-type calcium channels and insulin resistance on the cellular level[75].

However, not all members of the CCB class have the same effect on glucose homeostasis. Indeed, azelnidipine has been associated with beneficial effect on glucose homeostasis in a diabetic animal model[76]. Moreover, similar beneficial effects were seen in a small study in non-diabetic patients ($n$ = 17) with essential hypertension who had controlled blood pressure levels using amlodipine (5 mg/d)[77]. Azelnidipine (16 mg/d) or amlodipine (5 mg/d) was administered in a crossover design for 12-wk. Despite similar blood pressure reduction, azelnidipine significantly decreased levels of glucose and insulin 120 min after the 75 g oral glucose tolerance test (OGTT) ($P$ < 0.05 *vs* amlodipine). This effect may be associated with the anti-inflammatory effects of azalnidipine[78], since proinflammatory cytokines have been associated with impaired glucose tolerance[79]. Furthermore, azelnidipine inhibits the enhancement of sympathetic nervous activity[80]. Since the activation of the sympathetic nervous system has been associated with insulin resistance[66], azalnidipine treatment may contribute to the amelioration of insulin resistance.

Another interesting member of the CCB class is manidipine[81]. A beneficial effect on insulin resistance has been shown with manidipine treatment[82]. The beneficial effects of manidipine have been observed in both non-diabetic and T2DM patients[83,84]. Furthermore, we have recently shown that manidipine can ameliorate the possible statin-associated increase in insulin resistance[85]. In a prospective, randomized, open-label, blinded endpoint study a total of 40 patients with impaired fasting glucose, mixed dyslipidemia, and stage 1 hypertension were included. Patients were randomly allocated to rosuvastatin (10 mg/d) plus olmesartan (20 mg/d) or manidipine (20 mg/d). After 3 mo, a significant increase in HOMA-IR index by 14% ($P$ = 0.02 *vs* baseline) was seen in the olmesartan plus rosuvastatin group. On the other hand, HOMA-IR index did not change in the manidipine plus rosuvastatin group ($P$ = NS *vs* baseline; $P$ = 0.04 *vs* olmesartan plus rosuvastatin group). This favorable effect of manidipine may be linked to the drug's capacity to partially activate the PPARγ which plays a major role in glucose metabolism[82]. Indeed, the effect of manidipine to activate PPARγ is about two-thirds of that of pioglitazone, a full PPARγ activator[82]. This partial activation of PPARγ may contribute to the avoidance of side effects commonly associated with thiazolidinediones treatment. Moreover, an increase of adiponectin levels (which are inversely associated with the development of insulin resistance and metabolic syndrome) has been observed with manidipine[86]. Furthermore, manidipine induces a smaller activation of the sympathetic nervous system, which can also play a role in the beneficial effects on glucose homeostasis. Indeed, when compared with other CCBs, manidipine is associated with lower levels of plasma norepinephrine[87].

## β-BLOCKERS

A number of studies have associated treatment with β-blockers as having a disadvantageous effect on glucose homeostasis[88-91]. Indeed, a prospective study of three cohorts, namely the Nurses' Health Study (NHS) I and Ⅱ and the Health Professionals Follow-up Study evaluated the association between the use of different classes of antihypertensive medications and the risk of T2DM incident[92]. Treatment with a β-blocker was associated with a greater risk for the development of diabetes. Similarly, in the Atherosclerosis Risk in Communities study β-blockers led to an increase of risk for new-onset T2DM (RR = 1.28; 95%CI: 1.04-1.57)[4]. A large meta-analysis of patients with hypertension ($n$ = 94492) treated with beta blockers evaluated the risk for the development of T2DM[93]. Beta-blocker therapy resulted in a 22% increased risk for new-onset T2DM (RR = 1.22, 95%CI: 1.12-1.33) compared with non-diuretic antihypertensive agents. On the other hand, a recent reanalysis of data from the NAVIGATOR trial showed that β-blockers were not associated with new onset diabetes (HR = 1.10, 95%CI: 0.92-1.31)[74].

However, not all members of the β blocker class have similar effect on glucose homeostasis. Indeed, carvedilol as well as nebivolol have shown a differentiation from the rest of the class[94,95]. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) study was a randomized, double-blind, parallel-group trial that compared the effects of carvedilol and metoprolol tartrate on glycemic control[96]. Patients ($n$ = 1235) with hypertension (> 130/80 mmHg) and T2DM that were already receiving RAS blockers were randomized to receive carvedilol (6.25-25 mg/twice daily) or metoprolol (50-200 mg/twice daily). Open-label hydrochlorothiazide and a dihydropyridine calcium antagonist were added, if needed, to achieve blood pressure target. While blood pressure control was similar between groups, a difference was seen regarding glucose effects. The HbA1c increased with metoprolol (by 0.15%; $P$ < 0.001) but not carvedilol (by 0.02%; $P$ = 0.65). Moreover, insulin sensitivity improved with carvedilol (9.1%; $P$ = 0.004) but not metoprolol (2.0%; $P$ = 0.48 *vs* baseline; $P$ = 0.004 between groups). Similarly, a study in subjects with metabolic syndrome compared nebivolol (5 mg/d) with metoprolol (100 mg/d)[97]. After 12-wk treatment both nebivolol and metoprolol had similarly decreased blood pressure and heart rate. However, metoprolol decreased insulin sensitivity compared with nebivolol ($P$ = 0.03).

### Mechanisms

Several possible mechanisms that may be responsible

for the disadvantageous effect of β-blockers have been described. Treatment with conventional β-blockers leads to an unopposed a1-activity which causes vasoconstriction and decreased blood flow to the muscles, which are an important organ in the regulation of glucose homeostasis[98,99]. As a result a decrease in insulin-stimulated glucose uptake would occur, leading to insulin resistance. Furthermore, β-blockers can also decrease the first phase of insulin secretion from pancreatic β cells[88,89]. In addition, treatment with β-blockers can also lead to weight gain[100]. Since increased body weight is strongly associated with insulin resistance[101], this effect of β-blockers can further deteriorate glucose homeostasis.

## DIURETICS

An important class of antihypertensive drugs is diuretics. This class includes loop diuretics such as furosemide, thiazide diuretics such as hydrochlorothiazide, thiazide-like diuretics such as chlorthalidone and potassium-sparing diuretics, such as amiloride, eplerenone and spironolactone.

A number of studies have associated diuretic treatment of hypertension as having a negative effect on glucose homeostasis[18,102]. Indeed, a meta-analysis of 22 clinical trials with 143153 nondiabetic patients evaluated the effects of various antihypertensive drug classes on diabetes incidence[43]. Treatment with diuretic was associated with increased risk for new onset diabetes compared with other antihypertensive treatments as well as placebo[43]. A long-term cohort study with initially untreated hypertensive subjects ($n$ = 795) evaluated new-onset diabetes incidence according to antihypertensive treatment[103]. Diuretic treatment was present in 53.5% of subjects that developed T2DM, compared with 30.4% of patients that did not develop diabetes ($P$ = 0.002). Moreover, diuretic treatment was an independent predictor of new onset diabetes ($P$ = 0.004). Furthermore, a recent reanalysis of data from the NAVIGATOR trial showed that diuretics were associated with an increased risk of new onset diabetes (HR = 1.23, 95%CI: 1.06-1.44)[74].

A post hoc subgroup analyses of the ALLHAT study among nondiabetic participants of the study who were randomized to receive chlorthalidone ($n$ = 8419), amlodipine ($n$ = 4958), or lisinopril ($n$ = 5034) evaluated the effects of antihypertensive treatment on glucose levels as well as new-onset diabetes[104]. Chlorthalidone treatment was associated with a greater risk for developing diabetes compared with the other 2 treatment regimens ($P$ < 0.001)[104]. The Systolic Hypertension in the Elderly Program (SHEP) was a placebo-controlled, double-blind, randomized, multicenter clinical trial that evaluated the efficacy of chlorthalidone in patients ($n$ = 4736) with isolated systolic hypertension[105]. After 3 years of treatment, the incidence of new-onset diabetes was similar between the chlorthalidone (8.6%) and placebo group (7.5%; $P$ = 0.25 between groups)[105]. However, when study participants were re-evaluated after a mean follow-up of 14.3 years, 13.0% of patients developed diabetes in the chlorthalidone group *vs* 8.7% in the placebo group ($P$ < 0.0001)[106].

Of note, chlorthalidone seems to be differentiated from the rest of the thiazide diuretics class[107]. Indeed, chlorthalidone has a different chemical structure compared with the rest of thiazide diuretics[107] as well as the ability to inhibit carbonic anhydrase[108]. Carbonic anhydrase regulates a number of CV related risk factors[109,110] and its activity is also directly proportional to increasing blood glucose concentration[111]. As a result, chlorthalidone may have a more favorable metabolic profile compared with the other thiazide diuretics[107].

The effects of amiloride on blood glucose levels were evaluated in a study by Stears *et al*[112]. Patients with essential hypertension ($n$ = 37) received, in random order, 4 wk of once-daily treatment with hydrochlorothiazide (25-50 mg), nebivolol (5-10 mg), combination (hydrochlorothiazide 25-50 mg and nebivolol 5-10 mg), amiloride (10-20 mg), and placebo. Each drug was force titrated at 2 wk and separated by a 4-wk placebo washout. Both amiloride and hydrochlorothiazide had similar changes in blood pressure reduction. However, an increase of glucose levels after a 2 h OGTT was observed with hydrochlorothiazide treatment, while no change was seen with amiloride ($P$ < 0.0001).

The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) evaluated the effects of eplerenone on new-onset diabetes mellitus in patients ($n$ = 1846) with mild heart failure[113]. After a follow-up of 21 mo, eplerenone had no effect on new-onset diabetes mellitus (HR = 0.94, 95%CI: 0.59-1.52). Another study compared the effects of eplerenone with spironolactone in patients ($n$ = 107) with mild chronic heart failure[114]. Spironolactone increased levels of HbA1c ($P$ < 0.0001), while no change was observed in the eplerenone group.

### Mechanisms

Among the possible mechanisms through which thiazide diuretics may affect glucose homeostasis, hypokalemia may play an important role[115]. Indeed, hypokalemia can lead to decreased insulin secretion by β cells in response to glucose, as well as decrease in blood flow in muscles. A quantitative review evaluating studies that used thiazide diuretics, found an inverse relationship between glucose and potassium with thiazide use[116]. Similar results were observed in an analysis of data from the SHEP study[117]. In the first year of the study among 3790 nondiabetic participants each 0.5-mEq/L decrease in serum potassium was independently associated with a 45% higher adjusted diabetes risk (95%CI: 24%-70%; $P$ < 0.001). However, a prespecified subgroup analysis of metabolic parameter data from patients participating in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) study did not confirm a relationship between hypokalemia and deterioration of serum glucose levels[118].

Moreover, a decrease in magnesium can be seen with diuretic treatment. This could also contribute to the dis-

advantageous effects of diuretics on glucose homeostasis, since hypomagnesaemia is an independent predictor of T2DM[119,120]. Furthermore, thiazide treatment is also associated with visceral fat redistribution, liver fat accumulation and low-grade inflammation, which in turn increase the risk of new-onset diabetes[121].

## OTHER ANTIHYPERTENSIVE DRUGS

There is little evidence about the effects of other, less used, antihypertensive drugs on glucose homeostasis. A randomized, double-blind multicenter study compared moxonidine (0.2-0.6 mg/d) with metoprolol (50-150 mg/d) in hypertensive subjects ($n$ = 127) with T2DM[122]. After 12 wk of treatment both groups had similar blood pressure reductions as well as similar HbA1c values. However, fasting plasma glucose decreased in the moxonidine group, while an increase was seen in the metoprolol group ($P < 0.05$). Furthermore, the HOMA-IR decreased with moxonidine in contrast to the increase observed with metoprolol. Another multicenter, prospective, randomized study compared moxonidine with metformin[123]. Patients older than 40 years old, with impaired glucose tolerance (or diabetes mellitus treated with diet alone) and a body mass index (BMI) of at least 27 kg/m$^2$ were treated twice daily with moxonidine 0.2 mg or metformin 500 mg for 16 wk. Compared with metformin, moxonidine decreased the area under the curve for insulin ($P = 0.049$). On the other hand, only metformin significantly decreased fasting plasma glucose ($P < 0.05$ *vs* baseline and *vs* moxonidine) as well as HbA1c ($P < 0.005$ *vs* baseline). Both treatments similarly increased the Matsuda ISI from baseline to a comparable degree ($P < 0.05$ *vs* baseline for both groups). Another randomized open parallel study evaluated the chronic effects of moxonidine *vs* amlodipine in obese hypertensive patients ($n$ = 40)[124]. Plasma levels of insulin 120 min after glucose load, decreased with moxonidine treatment ($P < 0.05$) while no change was seen with amlodipine. A multinational, open-label, observational study, the Moxonidine Efficacy on blood pressure Reduction revealed in a metabolic SYndrom population (MERSY) study evaluated the effects of moxonidine on serum metabolic parameters[125]. Patients with hypertension received moxonidine (0.2-0.4 mg/d) either as monotherapy or as adjunctive therapy for 6 mo. A beneficial trend in metabolic parameters such as fasting plasma glucose and body weight was observed with moxonidine.

A small study evaluated the effects of doxazosin in hypertensive non-insulin depended diabetic patients[126]. Doxazosin significantly improved insulin sensitivity during the euglycemic insulin clamp and enhanced OGTT. Similarly another small study showed a beneficial effect of doxazosin (2 mg or 4 mg daily for 3 mo) on insulin resistance indices in hypertensive patients ($n$ = 21) with T2DM .

## CONCLUSION

Hypertension is associated with increased morbidity and mortality. Furthermore, hypertensive patients have an increased prevalence of insulin resistance as often is the case with metabolic syndrome subjects. This disturbance in glucose homeostasis further increases the risk for the development of CVD as well as the development of diabetes. The various antihypertensive drug categories have different effects on glucose metabolism. Indeed, ACE-I and ARBs have the most favorable effect on insulin resistance and the development of T2DM. Moreover, CCBs have an overall neutral metabolic effect. However, both azelnidipine and manidipine have been associated with beneficial glucose effects. On the other hand, diuretics as well as β-blockers have been associated with detrimental effects on glucose metabolism.

An interesting query is whether the adverse effects of some antihypertensive drug categories on glucose metabolism and their potency to increase new-onset diabetes mellitus incidence is also associated with an increase in CVD events. It would be reasonable to assume that the drug-induced increases in glucose levels and T2DM incidence would have increased CVD risk similarly to traditional risk factors for new-onset diabetes. However, no such increase in CVD risk was seen in the ALLHAT study in those who developed diabetes in the chlorthalidone treatment arm[127]. Similarly were the results from the SHEP study[106]. Diabetes at baseline was associated with increased CV mortality rate (adjusted HR = 1.659, 95%CI: 1.413-1.949) and total mortality rate (adjusted HR = 1.510, 95%CI: 1.347-1.693). Furthermore, diabetes that developed during the trial among subjects on placebo was also associated with increased CV adverse outcome (adjusted HR = 1.562, 95%CI: 1.117-2.184) and total mortality rate (adjusted HR = 1.348, 95%CI: 1.051-1.727). However, diabetes that developed among subjects during diuretic therapy did not have statistically significant associations with CV mortality rate (adjusted HR = 1.043, 95%CI: 0.745-1.459) or total mortality rate (adjusted HR = 1.151, 95%CI: 0.925-1.433). In addition, diuretic treatment in diabetic patients was strongly associated with lower long-term CV mortality rate (adjusted HR = 0.688, 95%CI: 0.526-0.848) and total mortality rate (adjusted HR = 0.805, 95%CI: 0.680-0.952). Of note, even if new-onset T2DM after diuretic or β-blocker is not associated with increased CVD morbidity and mortality, the health care cost should be considered. Indeed, the management and treatment costs of a hypertensive patient with diabetes are far greater compared with a non-diabetic patient.

On the other hand, the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale study, a long-term cohort study in initially untreated hypertensive subjects with a median follow up of 6 years, identified diuretic treatment as an independent predictor of new onset diabetes ($P = 0.004$)[103]. Of interest, CV event risk was similar between diabetic subjects at study baseline and subjects that developed new-onset T2DM during the study. An interesting study, evaluated hypertensive subjects ($n$ = 754) and followed them long term for 25-28 years[128]. Patients were treated with thiazide diuretics and beta-adrenergic blocking drugs with the addition of hydralazin during

the first decade. Calcium antagonists were substituted for hydralazin and, if needed, ACE-I were added when these drugs became available. After 25 years, treatment with β-blockers was associated with new-onset T2DM. New-onset diabetes was associated with an increased risk for stroke (HR = 1.67; 95%CI: 1.1-2.6; $P < 0.05$), myocardial infarction (OR = 1.66; 95%CI: 1.1-2.5; $P < 0.05$) and mortality (OR = 1.42; 95%CI: 1.1-1.9; $P < 0.05$). The mean observation time from onset of diabetes mellitus to a first stroke was 9.1 years and to a first myocardial infarction 9.3 years.

Despite the various effects of different antihypertensive drugs on glucose homeostasis, the overall expected benefits *vs* the potential risks should always be carefully weighted for each individual patient. As a result, when the benefits for a patient that should receive a treatment with an antihypertensive class with unfavorable glucose profile are greater than the risk of increased insulin resistance, then the glycemic effects of the antihypertensive drug should not disqualify the patient from treatment. Furthermore, there is often some diversity among the members of an antihypertensive class regarding their effect on glucose. As a result, the antihypertensive drug with the least adverse effect on glucose can be selected. Indeed, despite the overall adverse effect of the β-blockers families on glucose homeostasis, newer members of the class, such as carvedilol and nebivolol, have shown that they are clearly different from the rest regarding glucose effects.

Overall, when treating hypertensive patients the physician should carefully assess the individual patient' s medical history which often dictates a particular treatment. When there are no contraindications, an antihypertensive drug with a favorable or at least neutral effect on glucose homeostasis should be selected. This way, any beneficial effects of lowering blood pressure would not be shadowed in any way by a worsening of the metabolic profile. Patients with a strong indication for receiving a β-blocker or a diuretic should not be disqualified only because of the negative effect of these drug categories on glucose homeostasis. When a drug with negative effects on glucose homeostasis is selected, the physician should have in mind the possible deterioration of glucose metabolism and increased risk for new-onset diabetes and thus follow-up the patient accordingly.

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