Review article

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An overview of the effects of combination therapy with a renin-angiotensin system blocker plus a calcium channel blocker on glucose homeostasis in non-diabetic hypertensive patients

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ABSTRACT

Arterial hypertension (AH) is a major cardiovascular risk factor and often coexists with insulin resistance. Insulin resistance impairs glucose homeostasis and has been associated with the development of new-onset type 2 diabetes mellitus (T2D). Overactivity of renin-angiotensin system (RAS) mediated by angiotensin II adversely affects glucose homeostasis. The blockade of RAS with the use of angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) has been associated with beneficial effects on glucose metabolism. On the other hand, calcium channel blockers (CCBs) have been reported to exert a metabolic neutral effect. By contrast, the use of diuretics and beta-blockers has been shown to have an overall negative effect on glucose metabolism. Current ESH/ESC treatment guidelines recommend the use of fixed single-pill combinations of RAS blockers with either CCBs or thiazide/thiazide-like diuretics in hypertensive patients with grade 1 AH and high cardiovascular risk, or greater. Nonetheless, considering the patient's medical history and comorbidities, antihypertensive treatment should be carefully tailored. To this, hypertensive patients at risk of developing new-onset T2D, with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), should be preferentially treated with either monotherapy or combined treatment using agents which do not affect or worsen glucose homeostasis.

KEY WORDS: *Arterial hypertension, calcium channel blocker, impaired fasting glucose, impaired glucose tolerance, renin-angiotensin-system blocker*

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INTRODUCTION

Patients with arterial hypertension (AH) often present with impaired glucose metabolism and/or insulin resistance[1,2] which is associated with an increased risk of developing type 2 diabetes mellitus (T2D)[3].

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Individuals with impaired glucose metabolism have been identified by the American Diabetes Association (ADA) between normoglycemia and T2D, including those with impaired fasting glucose (IFG) or impaired glucose tolerance (IFG)[4]. The prevalence of AH is higher among individuals with IFG or IGT compared with those with normoglycemia[5-7].

Different classes of antihypertensive drugs exert various effects on glucose homeostasis[8]: renin-angiotensin system (RAS) blockers, including angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), have been shown to have beneficial effects on glucose homeostasis; calcium channel blockers (CCBs) have an overall neutral effect[9]. By contrast, thiazides and beta-blockers have been associated with negative effects as well as the development of new-onset T2D.

Recent guidelines by ESH/ESC advocate the use of fixed singe-pill combinations of RAS blockers with CCBs or with thiazide/thiazide-like diuretics as first line therapy in hypertensive patients with grade 1 AH and high cardiovascular risk, or greater[10,11]. Nonetheless, treatment strategy of AH should take into consideration any adverse effects of the agents used on glucose metabolism and the incidence of new-onset T2D[12].

AIM

This review discusses the available information regarding the effect of commonly used RAS blockers, CCBs and their combinations on indices of glucose homeostasis and the incidence of new-onset T2D, in non-diabetic patients with AH. The foreground question is shown by PICO statement[13] in Table 1.

MATERIALS AND METHODS

A literature review was conducted focusing on the effect of antihypertensive agents and their combinations on glucose homeostasis. We studied papers discussing the effects of ARBs, ACEi or CCBs and their combinations; ARB/CCB and ACEi/CCB. Literature research was performed using PUBMED and MEDLINE, with the following Medical Subjects Headings terms (MeSH) and keywords: "antihypertensive treatment", "combination of ARB and CCB", "combination of ACEi and CCB", "carbohydrate metabolism", "glucose metabolism", "glucose homeostasis", "prediabetes", "impaired fasting glucose", "IFG", "impaired glucose tolerance", "IGT", "insulin sensitivity", "insulin resistance", "HOMA-IR", "new-onset T2D". Randomized controlled trials, original papers, review articles and meta-analyses were included. The refer-

TABLE 1. PICOT statement.

PICOT statement		
P	Patient / Population	Non-diabetic patients with AH
I	Intervention / Indicator / Exposure	RAS blockers and/or CCBs
C	Compare / Control	Placebo, drug monotherapy, combination treatment
O	Outcome	New-onset T2D, effect on indices of glucose metabolism
T	Type of Study or Question	Narrative review

AH; arterial hypertension, RAS; renin-angiotensin system, CCBs; calcium channel blockers, T2D; type 2 diabetes mellitus

ABBREVIATIONS: *ACEi: angiotensin converting enzyme inhibitor, ADA: American Diabetes Association, AH: arterial hypertension, ARB: angiotensin receptor blocker, BB: beta-blocker, BP: blood pressure, CCB: calcium channel blocker, DBP: diastolic blood pressure, ESH: European Society of Hypertension, ESC: European Society of Cardiology, FPG: fasting plasma glucose, HbA1c: Hemoglobin A1c, HOMA-IR: homeostatic model assessment for insulin resistance, HCTZ: hydrochlorothiazide, IFG: impaired fasting glucose, IGT: impaired glucose tolerance, INS: fasting insulin, OGTT: oral glucose tolerance test, PPAR-γ: peroxisome proliferator activated receptor-γ , RAS: renin-angiotensin system, RCTs: randomized controlled trials , SBP: systolic blood pressure, T2D: type 2 diabetes mellitus, TD: thiazide diuretic, QUICKI: quantitative insulin-sensitivity check index*

ABBREVIATIONS OF TRIAL NAMES: *ACCOMPLISH: Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension, ADaPT: ACEi-based versus diuretic-based antihypertensive primary treatment in patients with pre-diabetes, ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack trial, ASCOT-BPLA: Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm, CAMUI: Combination of antihypertensive therapy in the elderly, multicenter investigation , CAPP: Captopril Prevention Project , CHARM programme: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity programme, CHARM-Added: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity-Added , CHARM-Alternative: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity-Alternative, CHARM-Preserved: Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity-preserved, DREAM: the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication , DREAM On: Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up, HOPE: Heart Outcomes Prevention Evaluation study, INVEST: The International Verapamil-Trandolapril Study , LIFE: Losartan Intervention For Endpoint reduction in hypertension, NAVIGATOR: Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research, ONTARGET: Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, PRoFESS: Prevention Regimen for Effectively Avoiding Second Strokes, SCOPE: the Study on Cognition and Prognosis in the Elderly , STAR: Study of Trandolapril/Verapamil SR And Insulin Resistance , TRANSCEND: Telmisartan Randomized Assessment Study in ACEi Intolerant Subjects with Cardiovascular Disease, VALUE: Valsartan Antihypertensive Long-term Use Evaluation trial*

ences of these articles were scrutinized for relevant articles. For articles not written in English, only the abstracts were considered. Articles with results regarding only diabetic population of patients were excluded from the analysis.

Figure 1 provides a flow diagram of the selected process and articles included in the analysis.

RESULTS

Comparative trials of drug combinations included in this review are summarized in Table 2.

Renin-angiotensin system (RAS) blockers

Glucose homeostasis and RAS are strongly associated. Overactivity of RAS, mediated by angiotensin II, results in insulin resistance, and eventually may lead to T2D[14]. Several trials have identified a beneficial effect of RAS blockers on glucose metabolism.

Angiotensin converting enzyme inhibitors, ACEi

Treatment with ACEi was associated with a lower incidence of new-onset T2D in clinical trials showing an overall favorable effect on glucose metabolism.

In HOPE (n=9,279)[15] and CAPPP trials (n=10,985)[16], treatment with an ACEi (ramipril vs. placebo and captopril vs. diuretic or beta-blocker, respectively), resulted in a reduction of T2D incidence (-34%, p<0.001 and 21%,

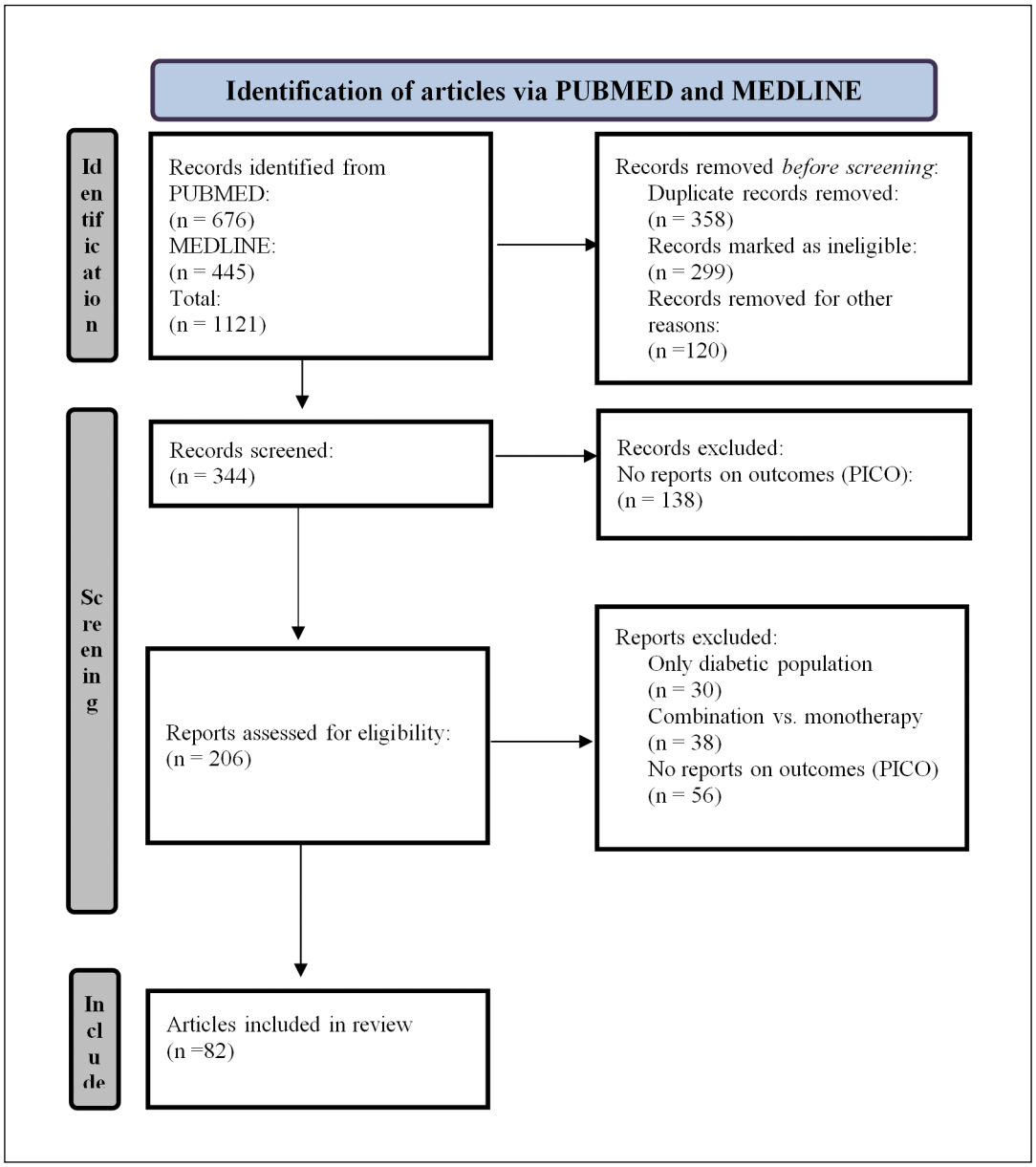

FIGURE 1. Flow diagram of the selected process and articles included in the analysis.

TABLE 2. Trials of combination treatment comparisons

Author	Year	Name	Study design	Total population	Diabetic status	Follow-up (weeks)	1st treatment group	2nd treatment group	Outcome: New-onset T2D		Outcome: Glucose homeostasis (group 1 vs group 2)
Dahlöf et al. (67)	2000	ASCOT-BPLA	Parallel	19,257	Mixed	66	ACEi+CCB	BB+TD	favors 1st group	HR: 0.70	favors 1st group: decrease in FPG levels
Zidek et al. (68)	2006	ADaPT	Parallel	2,011	IFG/IGT	48	ACEi+CCB	TD+BB	favors 1st group	24.3% vs. 29.0%, p<0.05	favors 1st group over 2nd group: in FPG, HbA1c levels change
Bakris et al. (69)	2006	STAR	Parallel	240	non-T2D	52	ACEi+CCB	ACEI+TD	favors 1st group	11.0% vs. 26.6%; p=0.002	favors 1st group: decrease in 2-h OGTT, FPG, insulin levels no change in QUICKI levels
Fogari et al. (70)	2008	-	Parallel	88	non-T2D	24	ACEi+CCB	ARB+TD	NA	NA	favors 1st group: decrease in insulin levels
Shimosawa et al. (74)	2007	-	Parallel	36	Mixed	16	ARB+CCB	ARB+TD	NA	NA	favors 1st group over 2nd group: increase of HbA1c levels in group 2
Pareek et al. (80)	2010	-	Parallel	148	Mixed	12	ARB+CCB	CCB+BB	NA	NA	both groups: no change in FPG or HbA1c levels
Martinez-Martin et al. (71)	2011	OLAS	Parallel	120	non-T2D	78	ARB+CCB	ARB+TD	favors 1st group	5% vs 18.3% OR: 4.24	favors 1st group: decrease in FPG, insulin and HOMA-IR levels
Christogiannis et al. (73)	2013	-	Parallel	60	non-T2D	16	ARB+CCB	ARB+TD	NA	NA	both groups: no change in HOMA-IR, or FPG or HbA1c levels
Nishiwaki et al. (76)	2013	-	Parallel	86	Mixed	48	ARB+CCB	ARB+TD	NA	NA	both groups: no change in FPG or HbA1c levels
Sato et al. (77)	2013	-	Parallel	142	Mixed	12	ARB+CCB	ARB+TD	NA	NA	both groups: no change in FPG or HbA1c levels
Oshikawa et al. (75)	2014	-	Parallel	196	Mixed	12	ARB+CCB	ARB+TD	NA	NA	favors 1st group over 2nd group: increase of FPG and HbA1c levels in group 2
Suh et al. (78)	2014	-	Parallel	199	Mixed	8	ARB+CCB	ARB+TD	NA	NA	both groups: no change in FPG levels
Toyoda et al. (79)	2015	-	Parallel	87	Mixed	12	ARB+CCB	ARB+TD	NA	NA	both groups: no change in FPG or HbA1c levels
Motozato et al. (81)	2016	EXAMINER	Parallel	52	Mixed	16	ARB+CCB	ARB+CCB	NA	NA	both groups: no change in FPG or HbA1c levels
Huo et al. (72)	2019	CHINA STATUS III	Observa-tional	985	Mixed	52	ARB+CCB	-	low incidence	0.6%	NA

T2D; type 2 diabetes mellitus, IFG; impaired fasting glucose, IGT; impaired glucose tolerance, FPG; fasting plasma glucose, HOMA-IR; homeostatic model assessment for insulin resistance, Hemoglobin A1c, ACEi; angiotensin-converting enzyme inhibitor, ARB; angiotensin-receptor blockers, CCB: calcium channel blocker, TD; thiazide diuretic, BB; beta-blocker, HbA1c; Hemoglobin A1c

p<0.01, respectively). Similar results were shown in the ALLHAT trial (n=33,357). In ALLHAT, a risk reduction of new-onset T2D was associated with lisinopril treatment vs. chlorthalidone or amlodipine treatment (-30%, p<0.001, -17%, p<0.01, respectively)[17].

The overall favorable effect of ACEi was also reported by large meta-analyses. In a meta-analysis of 10 randomized controlled trials (RCTs, n=75,950), the use of ACEi was associated with a lower incidence of T2D vs. placebo (OR: 0.77; p<0.001)[18]. Similarly, in two network meta-analyses (including 224,140 and 224,832 subjects, respectively), ACEi were associated with a risk reduction of new-onset T2D vs. placebo (-22% and -18%, respectively)[19,20]. Another meta-analysis showed that ACEi treatment reduced the incidence of new-onset T2D (OR: 0.80, CI: [0.71, 0.91]) vs. other agents (beta-blockers, diuretics, CCBs or placebo)[21].

Concerning patients with IFG or IGT, small trials evaluated the effect of ACEi on glucose homeostasis. Delapril (among ACEi) improved insulin sensitivity in hypertensive patients with IGT[22,23].

Of note, in DREAM trial (n=5,269), ramipril (another ACEi member) had a neutral effect on glucose homeostasis[24]. Although, ramipril among patients with IFG or IGT did not reduce the incidence of new-onset T2D, it led to regression to normal glucose levels (p=0.001)[21,24]. However, this finding was not confirmed by the extension of DREAM trial[25].

Angiotensin receptor blockers, ARBs

Large clinical trials evaluated the effect of ARB treatment on glucose homeostasis; an overall beneficial effect was shown. Various ARBs decreased the incidence of new-onset T2D in several large RCTs, while others exerted a neutral effect.

Treatment with valsartan in VALUE (n=15,245) and NAVIGATOR trials (n=9,518) resulted in a lower incidence of new-onset T2D vs. placebo (HR: 0.86; p<0.001)[26] and vs. amlodipine (HR: 0.77; p<0.001)[27], respectively. Losartan was also associated with a reduction of new-onset T2D vs. atenolol (HR: 0.75; p=0.001), in LIFE trial (n=9193)[28].

Candesartan treatment vs. placebo showed an overall lower incidence of T2D (HR: 0.78; CI: [0.64, 0.96], p=0.02), in the CHARM-overall programme (n=7,599)[29]. The incidence of T2D was lower in only one arm (CHARM-Preserved) of this trial (OR: 0.60; CI: [0.41, 0.86]; p=0.005)[30]. In the CHARM-Added and CHARM-Alternative arms, candesartan did not show a difference on new-onset T2D (p=0.25)[31,32]. Similarly, a non-significant difference on new-onset T2D was observed among candesartan vs. placebo, in elderly patients in SCOPE trial (n=4,964)[33].

The effect of telmisartan was assessed by 3 major trials. In the TRANSCEND (n=5926)[34,35] and PRoFESS trials (n=20,332)[36], telmisartan showed a trend in reducing new-onset T2D vs. placebo (20.1% vs 21.6%; HR: 0.91 CI: [0.79, 1.05]; p=0.203 and 1.2% vs 1.5%; p=0.1, respectively). In the ONTARGET trial, telmisartan vs. ramipril did not show a difference in this outcome (6.7% vs. 7.5%, HR: 1.12; CI: [0.97, 1.29]) [40].

However, meta-analyses of these trials showed different results. A meta-analysis of LIFE, SCOPE and VALUE trials associated treatment with ARBs with a clinically significant reduction in the occurrence of new-onset T2D (RRR: 0.80, CI: [0.74, 0.86]; p<0.0001)[37]. Similar results were shown in the meta-analysis of TRANSCEND and PRoFESS trials. Telmisartan reduced the risk of new-onset T2D vs. placebo by approximately 16% (OR: 0.84 CI: [0.72, 0.97]; p<0.05)[38].

It has been shown that some ARBs possess peroxisome proliferator activated receptor-γ (PPAR-γ) partial activating properties and may favorably affect glucose metabolism. Several trials and meta-analyses evaluated the effects of ARBs on indices of glucose homeostasis, in patients with impaired glucose metabolism: In small trials, treatment with valsartan (although a non PPAR-γ activator) in non-diabetic hypertensive patients resulted in a reduction of fasting insulin levels and HOMA-IR[39,40]. On the other hand, treatment with irbesartan and telmisartan (documented with PPAR-γ activity) was associated with improvement on glucose metabolism[41-43]. Treatment with telmisartan, also improved HOMA-IR in several trials in non-diabetic patients[44-47]. In a study by Rizos et al., telmisartan improved insulin resistance indices compared with other ARBs in hypertensive pre-diabetic patients[48]. Moreover, the study showed that telmisartan retained its beneficial effects on glucose homeostasis even after combination with rosuvastatin (a statin associated with the development of T2D)[48]. Since hypertension is often accompanied with hyperlipidemia and thus antihypertensive drugs are often co-administered with statins the results of the previous study become even more relevant in clinical practice.

Of note, a meta-analysis showed that telmisartan was superior to other ARBs in improving HOMA-IR (mean difference: -0.23, CI: [-0.40 -0.06])[49]. Another meta-analysis of 11 RCTs with non-diabetic patients (n=59,862) compared ARBs to other classes of antihypertensive drugs. Treatment with ARBs was associated with significant reduction in the risk of new-onset T2D vs. placebo (OR: 0.83, CI: [0.78, 0.89]), beta-blockers (OR: 0.73, [0.62, 0.87]), CCBs (OR: 0.76, [0.68, 0.85]) and non-ARBs (OR: 0.57, [0.36, 0.91])[50]. ARBs were also associated with significant reduction in the risk of new-onset T2D, in patients with IGT (OR: 0.85, [0.78, 0.92])[50].

ARBs vs. ACEi

Data from a retrospective cohort study (n=20,108) showed that ACEi and ARBs were associated with a similar risk of new-onset T2D during a 6-year follow-up (OR: 0.92)[51], while in another retrospective study of normoglycemic patients with AH, ACEi treatment vs. ARBs resulted in a greater risk reduction of new-onset T2D (HR: 0.54, CI: [0.29, 0.99]; p=0.049)[52]. Similarly, in a meta-analysis (n=1,015), ACEi were superior on HOMA-IR improvement vs. ARBs in the long-term intervention subgroup of patients (mean difference: 0.41, CI: [0.06, 0.76]; p=0.022)[53].

Calcium channel blockers, CCBs

CCBs are generally considered to have an overall neutral metabolic profile[9]. Although not initially shown, results from a re-analysis of the NAVIGATOR trial, concluded that treatment with CCB (amlodipine) was not associated with the occurrence of T2D (HR: 0.95; CI: [0.79, 1.13])[54]. Similarly, a meta-analysis of 10 RCTs (n=108,118) in non-diabetic patients with AH, showed that the overall risk of T2D with CCBs was not significant (RR: 0.99, CI: [0.85, 1.15])[55].

Small size randomized trials evaluated the effect of treatment with CCBs in changes on indices of glucose metabolism. In these trials, amlodipine (among CCBs) exerted a neutral or a minor favorable effect[8,56-60]. On the other hand, manidipine (a newer CCB) through partial activation of PPAR-γ[61,62] has been associated with improvement on HOMA-IR[57,60,63]. Manidine treatment decreased HOMA-IR vs. clinidipine and amlodipine (all, p<0.05) in obese patients[60] and vs. amlodipine (-21.3%, p=0.007, vs. 8.3%, p=0.062) in patients with the metabolic syndrome[63]. It has been also shown that manidipine ameliorates the possible insulin resistance associated with statin therapy[62], thus favoring glucose homeostasis.

CCBs vs. RAS blockers

Data analysis from large RCTs have shown a clear overall superiority of RAS blockade vs. CCBs treatment.

A meta-analysis of five clinical trials compared the efficacy of ARBs and CCBs on HOMA-IR in non-diabetic patients[64]. Treatment with ARBs reduced HOMA-IR (mean difference: -0.65, CI: [-0.93 -0.38]) and fasting insulin (mean difference: -2.01, CI: [-3.27 -0.74]) vs. CCBs[64]. In another meta-analysis CCBs were associated with a higher incidence of T2D vs. ACEi (RR: 1.23; CI: [1.01, 1.51]) and ARBs (RR: 1.27; CI: [1.14, 1.42])[55].

This favorable effect of RAS blockers vs. CCBs was shown in a meta-analysis of 22 trials in primary and secondary prevention (n=145,939)[65,66]. Treatment with ACEi or ARBs reduced the risk of new-onset T2D (RR: 0.84; CI: [0.76, 0.93] and RR: 0.84; CI: [0.76, 0.92], respectively), whereas CCBs had a neutral effect (RR: 1.02; CI: [0.92, 1.13])[65,66].

RAS blockers - CCBs combination vs. other combinations on glucose homeostasis and new-onset T2D

ACEi/CCBs combination

Several comparative trials on the effect of different ACEi/CCBs combinations vs. other antihypertensive drugs combinations assessed the effects on glucose homeostasis and the incidence of new-onset T2D.

In the ASCOT-BPLA trial (n=19,257), the incidence of new-onset T2D was lower in the amlodipine/perindopril vs. atenolol/bendroflumethiazide combination (567 vs 799 cases; HR: 0.70, CI: [0.63, 0.78]; p<0.0001)[67]. Similarly, the open non-randomized observational ADaPT trial (n=2,011) showed that the prevalence of new-onset T2D was higher (24.3% vs. 29.0%; p<0.05) in the group of diuretic monotherapy or combination therapy with beta-blocker vs. ACEi or ACEi/CCB combination (ramipril monotherapy or plus felodipine)[68]. In the STAR trial, new-onset T2D, was less frequent in trandolapril/verapamil vs. losartan plus hydrochlorothiazide (HCTZ) combination (11.0% vs. 26.6%, p=0.002)[69].

Data regarding the effect of ACEi/CCB combination on indices of glucose metabolism are scarce. In the STAR trial, ACEi/CCB combination was superior to ARB plus diuretic on glucose tolerance in hypertensive patients with IGT. In this trial, trandolapril/verapamil decreased the 2-hour oral glucose tolerance test (OGTT) levels vs. losartan/HCTZ (-0.2±0.2 mmol/L; p=0.329 vs. +1.4±0.4 mmol/L; p<0.001; between groups, p<0.001)[69]. Although FPG and HbA1c levels were increased in both treatment arms, trandolapril/verapamil was associated with minor increases (0.24±0.23 vs. 0.76±0.22 mmol/L, p=0.087 and 0.1±0.1 vs. 0.4±0.1%, p=0.027, respectively). Furthermore, in this trial, insulin sensitivity, assessed by quantitative insulin-sensitivity check index (QUICKI), was decreased by losartan/HCTZ (0.000±0.001 vs. 0.005±0.001; p=0.016)[69]. Improvement on insulin sensitivity was also observed in another comparative trial (n=88) of delapril/manidipine vs. olmesartan/HCTZ combination, in obese hypertensive patients[70]. CCB-based combination increased insulin sensitivity (glucose infusion rate [GIR] mg/kg/min) by 3.01 mg/min/kg, (vs. baseline, p=0.038; between groups, p<0.05,)

and decreased plasma insulin by 17.8 pmol/L (vs. baseline, p=0.047; between groups, p<0.05)[70]

ARBs/CCBs combination

A small number of trials examined the effect of ARB/CCBs vs. other combinations, mainly ARB plus thiazide diuretic (TD), on indices of glucose homeostasis and new-onset T2D.

New-onset T2D was a secondary endpoint in the OLAS trial (n=120)[71]. In this trial, the incidence of new-onset T2D was higher in the olmesartan/HCTZ group vs. olmesartan/amlodipine group (18.3% vs. 5%, OR: 4.24)[71]. In the CHINA STATUS III study, (n=985) the incidence of new-onset T2D was low (0.6%, n=5) with ARB/CCB combination (valsartan/amlodipine), in a 1-year follow-up[72].

Comparative trials on HOMA-IR are limited. A small trial (n=60) evaluated the effect of valsartan/amlodipine vs. valsartan/HCTZ combination on glucose metabolism indices (FPG, insulin, and HOMA-IR)[73]. Both treatments, resulted in no significant changes in glucose homeostasis, overall[73]. Of note, valsartan/amlodipine combination increased HOMA-IR by 0.1 unit (0.8[0.4-3.0] vs. 0.9[0.4-3.7]) at the end of treatment period[73]. On the other hand, the OLAS trial showed a clear superiority of olmesartan/amlodipine vs. olmesartan/HCTZ on metabolic parameters. HOMA-IR and fasting insulin were significantly decreased only in the olmesartan/amlodipine group (24.1 and 25.0%, respectively; both, p<0.01)[71].

Results from other small trials regarding changes in HbA1c and/or FPG showed an overall favorable effect of ARB/CCBs vs. ARB/TD or ARB/beta-blocker combinations. In a trial by Shimosawa et al., an increase in HbA1c levels was observed with losartan/HCTZ vs candesartan/amlodipine (5.54±0.33% vs. 5.84 ±0.71%)[74]. On the other hand, Oshikawa et al. showed that losartan/HCTZ increased both HbA1c and FPG levels vs. losartan/amlodipine (p=NS)[75]. Similar results were also shown by several trials where both treatment comparators had overall similar neutral effects on FPG and HbA1c[76-79]. Combination of ARB/CCBs vs. ARB/beta-blocker also showed a neutral effect on glucose homeostasis[80].

The comparison between two different ARB/CCB combinations was evaluated in the EXAMINER trial (n=52)[81]. Both valsartan/amlodipine vs. irbesartan/amlodipine combinations had a neutral result, as they did not exert any changes in HbA1c and FPG levels[81].

In a meta-analysis (n=48,913), RAS blockers plus CCBs compared with other antihypertensive combinations, were associated with a significant decrease in FPG by 2.3 mg/dL (p=0.03) and a significant net decrease in HbA1c of 0.20% (p<0.001)[82].

Concluding remarks

This review indicates that the effect of ACEi and ARBs monotherapy yields an overall favorable effect on glucose homeostasis, while treatment with CCBs appear to be neutral. RAS blockade plus CCBs combination treatment may exert also favorable effects in non-diabetic patients and seems to prevent the progression to T2D.

The incidence of new-onset T2D or the effect on other indices of glucose homeostasis of these classes of hypertensive drugs was a prespecified primary or secondary endpoint only in a few trials (Table 2)[67-71]. Likewise, a rather limited number of trials were designed to evaluate the effect on glycemic indices of these combinations on patients with impaired glucose homeostasis (IFG or IGT)[69-71,73] (Table 2).

Despite these limitations in trial endpoints and design, it seems that ACEi/ARB plus CCBs combinations affect glucose metabolism in a positive way, mostly through their preserved separate drug action:

ACEi directly improve insulin sensitivity particularly in the skeletal muscle[83] while both ACEi and ARBs increase skeletal muscle blood flow through vasodilatation, thus improving insulin sensitivity. RAS blockers (mainly telmisartan and to a much lesser degree irbesartan) exert additional favorable effects, including partial PPAR-γ agonist action and protection against the oxidative action of angiotensin II[8,41-43]. RAS blockers have been shown to decrease sympathetic nervous system activation, thus further contributing to improvement of insulin sensitivity[9].

CCBs may improve insulin sensitivity through vasodilation in insulin-sensitive tissues and concomitant increased muscle blood flow[8]. These agents also decrease sympathetic nervous system activation and prevent inhibition of glucose transporters and glycogen synthase by calcium[8]. Additionally, it has been proposed that CCBs enhance pancreatic β-cell function and might inhibit their apoptosis[55]

Current guidelines for the prevention of diabetes are in favor of the use of a fixed single-pill combination of a RAS blocker with a CCB in patients with IFG or IGT. Using a thiazide diuretic (TD) or beta-blocker administration could be an alternative to CCBs in certain patient populations; beta-blocker in combination with a TD should be avoided due to its diabetogenic action[12] (Figure 2).

In conclusion, antihypertensive treatment should be individualized considering the patient's history and comorbidities. In this respect, impaired glucose metabolism dictates the selection of particular drugs over others; agents with a favor and/or a neutral effect should be preferentially used to mitigate the risk of new-onset T2D.

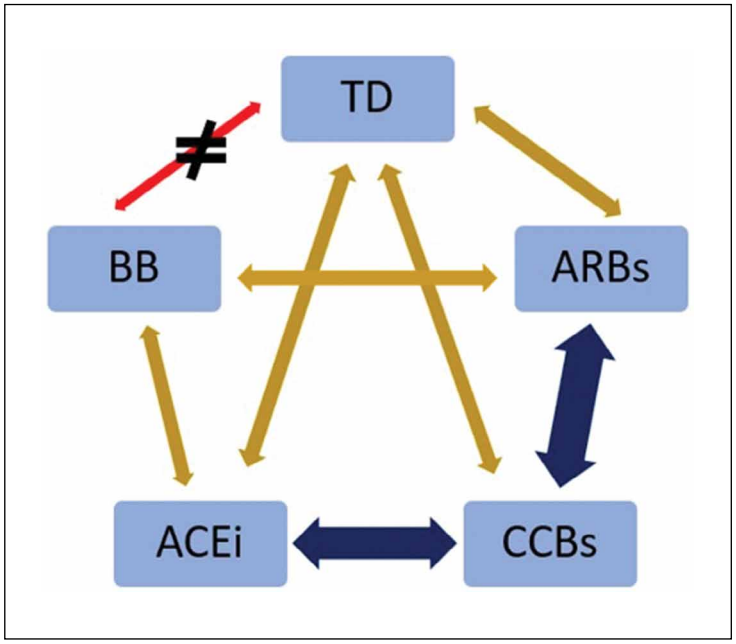

FIGURE 2. Possible combinations of drugs in hypertensive patients with impaired glucose homeostasis. Blue arrow: highly recommended. Yellow arrow: might be combined, Red arrow: not recommended.
ACEi; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blocker, BB; beta-blocker, CCB; calcium channel blocker, TD; thiazide diuretic

However, the overall expected benefits vs. the potential risks must always be carefully weighted for each individual patient (especially in selected patient subgroups such as those with established atherosclerotic cardiovascular disease, heart failure, uncontrolled BP etc.). As a result, when the benefits of antihypertensive treatment overweigh the risk of increased insulin resistance the patient should not be disqualified from receiving appropriate treatment with a drug associated with unfavorable glucose homeostasis.

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ΠΕΡΙΛΗΨΗ

Επισκόπηση των επιδράσεων της θεραπείας με συνδυασμό αναστολέα του συστήματος ρενίνης-αγγειοτενσίνης και αναστολέα διαύλων ασβεστίου στην ομοιοστασία της γλυκόζης σε μη διαβητικούς υπερτασικούς ασθενείς

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Η αρτηριακή υπέρταση (ΑΥ) αποτελεί σημαντικότατο τροποποιήσιμο παράγοντα καρδιαγγειακού κινδύνου, Συχνά στους υπερτασικούς ασθενείς συνυπάρχει αντίσταση των ιστών στην ινσουλίνη. Η αντίσταση στην ινσουλίνη έχει αρνητική επίδραση στην ομοιοστασία της γλυκόζης και μπορεί να οδηγήσει στην εμφάνιση σακχαρώδη διαβήτη τύπου 2 (ΣΔ2). Η υπερδραστηριότητα του συστήματος ρενίνης-αγγειοτενσίνης-αλδοστερόνης (ΣΡΑ), διαμέσου της δράσης της αγγειοτενσίνης ΙΙ έχει αρνητική επίδραση στην ομοιοστασία της γλυκόζης. Οι διάφορες κατηγορίες ανθυπερτασικών φαρμάκων ασκούν διαφορετικά αποτελέσματα σε αυτή την ομοιοστασία. Ο αποκλεισμός του ΣΡΑ μέσω είτε αναστολέων του μετατρεπτικού ενζύμου της αγγειοτενσίνης (α-ΜΕΑ) είτε αναστολέων των υποδοχέων της αγγειοτενσίνης ΙΙ (ΑΥΑ) έχει ευεργετικές επιδράσεις στο μεταβολισμό της γλυκόζης. Οι αποκλειστές διαύλων ασβεστίου (ΑΔΑ) θεωρούνται μεταβολικά ουδέτερα φάρμακα. Αντίθετα, τα θειαζιδικά διουρητικά και οι β-αναστολείς ασκούν συνολικά μια αρνητική επίδραση στο μεταβολισμό της γλυκόζης. Οι ισχύουσες κατευθυντήριες οδηγίες για τη θεραπεία της ΑΥ συνιστούν τη χρήση σταθερών συνδυασμών α-ΜΕΑ ή ΑΥΑ είτε με ΑΔΑ είτε με θειαζιδικά διουρητικά. Ωστόσο, η επιλογή της ανθυπερτασικής θεραπείας πρέπει γίνεται προσεκτικά για κάθε ασθενή λαμβάνοντας υπόψη το ιστορικό και τις συννοσηρότητες. Έτσι, στους υπερτασικούς ασθενείς με διαταραχή γλυκόζης νηστείας (IFG) ή διαταραχή της ανοχής στη γλυκόζη (IGT) που αποτελούν ομάδα υψηλού κινδύνου για εμφάνιση ΣΔ2 η ανθυπερτασική θεραπεία συστήνεται να περιλαμβάνει συνδυασμούς φαρμάκων που είτε δεν επηρεάζουν είτε βελτιώνουν τους δείκτες του μεταβολισμού της γλυκόζης και της πιθανότητας εμφάνισης ΣΔ2.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Αναστολείς του μετατρεπτικού ενζύμου της αγγειοτενσίνης, αναστολείς των υποδοχέων της αγγειοτενσίνης ΙΙ, αποκλειστές διαύλων ασβεστίου, ομοιοστασία γλυκόζης, σακχαρώδης διαβήτης τύπου 2*

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