MAEDICA – a Journal of Clinical Medicine
2022; 17(3): 561-570
https://doi.org/10.26574/maedica.2022.17.3.561

MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

The Effect of Commonly Used Fixed-Dose Single Pill Combinations of Renin-Angiotensin-System Blockers and Calcium Channel Blockers on HOMA-IR Index in Hypertensive Patients with Impaired Fasting Glucose: a 12-Week Randomized Open-Label Prospective Study

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ABSTRACT

Backround: *The effect of antihypertensive drugs on glucose homeostasis and insulin resistance remains an issue under investigation. There is evidence that renin-angiotensin system (RAS) blockers may favorably affect glucose metabolism, while treatment with calcium channel blockers (CCBs) is considered to have an overall neutral metabolic effect. However, the effects on glycemic indices may differ among agents within the same class of antihypertensive drugs.*

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Article received on the 27th of July 2022 and accepted for publication on the 26th of August 2022

Objective: *To evaluate the effects of different fixed-dose single pill combinations of RAS blockers with CCBs on homeostatic model assessment for insulin resistance (HOMA-IR).*

Methods: *Drug-naive patients with arterial hypertension (AH) and impaired fasting glucose (IFG) were randomly allocated to open-label fixed, single pill combinations of valsartan 160 mg/day plus amlodipine 5 mg/day (VAL/AMLO group, n = 54), delapril 30 mg/day and manidipine 10 mg/day (DEL/MANI group, n = 53) or telmisartan 80 mg/day and amlodipine 5 mg/day (TEL/AMLO group, n = 51) for 12 weeks. Glycemic indices and HOMA-IR were determined at baseline and post-treatment.*

Results: *A total of 158 patients were included. All treatment combinations effectively reduced blood pressure (systolic and diastolic) to similar levels (all $p < 0.001$). A decrease in the HOMA-IR index by 22.55% ($p < 0.01$) was noted following treatment with TEL/AMLO, while an increase by 1.4% ($p = 0.57$) and 12.65% ($p = 0.072$) was observed in the VAL/AMLO group and the DEL/MANI group, respectively. These changes were significantly different between TEL/AMLO and DEL/MANI ($p < 0.05$) as well as between TEL/AMLO and VAL/AMLO ($p < 0.001$).*

Conclusions: *Despite similar antihypertensive action, the effect of fixed, single pill combinations with TEL/AMLO, VAL/AMLO and DEL/MANI on insulin resistance is in favor of TEL/AMLO.*

Trial registration: *The study protocol was published online in https://diavgeia.gov.gr/ (No: ΒΘ6Σ46906Η-ΑΕΣ) via the Ministry of Digital Governance, after receiving approval from the Scientific Council and Administrative Council of University Hospital of Ioannina (No. of approval: 1/12-06-2014 (issue 150).*

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Keywords: arterial hypertension, RAS blockers, CCBs, glucose metabolism, HOMA-IR, IFG.

LIST OF ABBREVIATIONS

AH: arterial hypertension
BP: blood pressure
HBPM: home blood pressure monitoring
T2D: type 2 diabetes mellitus
IFG: impaired fasting glucose
IGT: impaired glucose tolerance
RAS: renin-angiotensin-system
ACEi: angiotensin converting enzyme inhibitors
ARB: angiotensin II receptor blockers
SBP: systolic blood pressure
DBP: diastolic blood pressure
BMI: body mass index
Glu: fasting serum glucose
INS: fasting insulin
HOMA-IR: homeostatic model assessment for insulin resistance
HbA_{1c}: Hemoglobin A_{1c}
ALT: alanine aminotransferase
AST: aspartate aminotransferase
PPAR-γ: peroxisome proliferator activated receptor-γ
GIR: glucose infusion rate
TEL/AMLO: telmisartan/amlodipine
DEL/MANI: delapril/manidipine
VAL/AMLO: valsartan/amlodipine

INTRODUCTION

The incidence of arterial hypertension (AH) is constantly increasing (1) and prevails as a major risk factor for stroke, coronary heart disease, heart failure, peripheral arterial disease, chronic renal failure and atrial fibrillation in both men and women (2-7). Despite the variety of antihypertensive agents with favorable safety and efficacy profile, the percentage of on-target treated patients with current guidelines remains low, especially with monotherapy (8). Fixed singe-pill dual combinations of renin-angiotensin-system (RAS) blockers (angiotensin converting enzyme inhibitors [ACEi] and angiotensin II receptor blockers [ARB]) with calcium channel blockers (CCBs) and/or a thiazide/thiazide-like diuretic are recommended by the European Society of Hypertension – ESH and European Society of Cardiology – ESC Guidelines 2018 as a preferable starting

treatment in patients with grade 1 AH or greater (9). The rationale leading to the preferable combination therapy when treating patients with AH originates from various long-term prospective studies that showed a greater effectiveness of dual or triple combination therapy in the management and adequate control of blood pressure (BP) (8). Thus, combination therapy using agents with different mechanism of action *vs.* monotherapy results in a decrease of cerebrovascular events by 54% *vs.* 40% and coronary events by 40% *vs.* 29% (10).

Individuals with AH often manifest additional cardiovascular risk factors such as dyslipidemia, carbohydrate metabolism disturbances, insulin resistance, obesity as well as type 2 diabetes (T2D) (11, 12).

Prediabetes is an intermediate stage between normal carbohydrate metabolism and T2D. This term includes two potentially overlapping groups: individuals with impaired fasting glucose (IFG) disorder, defined as a serum fasting glucose between 100-125 mg/dL (5.6-6.9 mmol/L), and individuals with impaired glucose tolerance (IGT), defined as serum fasting glucose concentration between 140-199 mg/dL (≥ 7.8 to < 11.0 mmol/L) two hours after a load with 75 g of glucose per os (13). Prediabetes is associated with presence of resistance in peripheral tissues to the action of insulin as well as dysfunction of pancreatic beta cells, disorders that occur before changes in glucose levels become detectable. Patients with essential hypertension have an increased prevalence of tissue insulin resistance (11, 12) and a 2.5 times higher risk of developing T2D compared to normotensive individuals (7). There is evidence that among antihypertensive treatment options, RAS blockers play an important role in prevention of new-onset T2D (14-16), CCBs have a neutral effect, while β-blockers and thiazide diuretics increase the risk of T2D (15, 16).

Telmisartan (among ARBs) and manidipine (among CCBs) have been reported to exert a favorable effect on insulin resistance (17-20).

Fixed combinations of RAS blockers with CCBs are broadly used in everyday clinical practice since they improve adherence and help achieving BP treatment goals. In the present study, we aimed to evaluate the effect of three commonly used fixed-combination of RAS blockers with a CCB on insulin resistance defined as alternations in the homeostatic model assessment for insulin resistance (HOMA-IR) index and other glucose homeostasis indices in hypertensive patients with IFG. ❑

MATERIALS AND METHODS

Study population

This is a randomized open label study of all eligible consecutive patients with personal medical history of AH, not on any antihypertensive treatment, and IFG at baseline attending the Outpatient Lipid and Hypertension Clinic of University Hospital of Ioannina, Greece, during a period of four years (2016 to 2020). Patients were randomly assigned 1:1:1 to valsartan/amlodipine 160/5 mg (VAL/AMLO group), delapril/manidipine 30/10 mg (DEL/MANI group) and telmisartan/amlodipine 80/5 mg (TEL/AMLO group) and followed up for 12 weeks.

Diagnosis of AH was defined as Systolic Blood Pressure (SBP) ≥ of 140 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 90 mm Hg according to the ESH/ESC Guidelines 2018 (9). For the diagnosis of AH, BP values were calculated from the average of more than two measurements of BP in sitting position under appropriate conditions at every scheduled visit. Based on the same guidelines, 24-h BP monitor and measurement of BP at home (home BP monitoring – HBPM) for seven consecutive days (two measurements in the morning and two in the evening) were also used for the diagnosis and classification of AH. Diagnosis of IFG was defined as serum fasting glucose of 100-125 mg/dL (5.6-6.9 mmol/L), according to 2014 American Diabetes Association guidelines (13).

Patient demographics, medical history, concomitant medications, anthropometric characteristics, and laboratory results were documented on two distinct visits: baseline visit and final visit after 12 weeks on dual antihypertensive treatment.

Compliance with study medication was assessed at 12 weeks. An 80% to 100% receipt of the prescribed number of tablets of their medication for each individual patient was considered as good compliance to study medication. Study medications were provided with reimbursement of 75% of the cost of any drugs prescribed through the Greek health care system. All participants gave their written informed consent be-

fore any clinical or laboratory evaluations were performed and before receiving any therapeutic interventions. The study protocol was approved by the Institutional Ethics Committee of University Hospital of Ioannina [Protocol Number: 5/26-3-2014 (issue: 25)].

Primary and secondary endpoints

The primary endpoint was change in the HOMA-IR index among groups. Secondary endpoints included changes in anthropometric variables (body weight, waist circumference, body mass index [BMI]), SBP, DBP, fasting serum glucose (Glu), fasting insulin (INS) and hemoglobin A1c (HbA1c).

Tolerability and safety were assessed by questioning all patients about adverse effects and monitoring relevant laboratory parameters (*e.g.*, creatinine levels, potassium, liver function tests).

Exclusion criteria

Patients with one of the following criteria were excluded from the study: 1) ischemic heart disease or any other vascular disease; 2) abnormal liver function tests (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) > three times the upper limit of normal range and/or a history of chronic liver disease); 3) alcohol use; 4) impaired renal function (serum Cre > 1.6 mg/dL and/or a history of chronic kidney disease [CKD], *i.e.* glomerulonephritis¸ chronic pyelonephritis, obstructive kidney disease); 5) T2D (treatment with antidiabetic medications or fasting glucose levels ≥ 126 mg/dL (≥ 7 mmol/L) in two separate measurements); 6) hypothyroidism (TSH > 5.0 μIU/mL); 7) antihypertensive treatment administration the last three months prior to study entry; 8) pregnant women or women not on adequate contraceptive measures.

Fasting blood samples were collected at every scheduled visit and laboratory reports were documented. All analyses were carried out at the Laboratory of Clinical Chemistry of the University Hospital of Ioannina under regular quality control procedures, including the use of reference pools and blinded duplicate samples. All laboratory determinations were carried out after an overnight fast. Insulin levels were calculated with immunological method using the microparticle Enzyme Immunoassay technique (Microparticle Enzyme Immunoassay, ABBOTT GmbH Diagnostika, Wiesbaden-Delkenheim, Germany). The HOMA-IR index was calculated as follows: HOMA-IR=fasting insulin (μIU/mL) *fasting glucose (mg/dL)/405 (21, 22).

Statistical analysis

The analyses were performed via the Statistical Package for Social Sciences (SPSS) 21.0 software (SPSS, IBM corp). Continuous numeric variables are expressed as mean ± standard deviation (SD) or median (interquartile: IQR) if Gaussian or non-Gaussian distributed, respectively. Categorical data are presented as total number (N) and percentage. Chi-squared test was used to compare categorical data among study groups. Correlations between parameters were evaluated using Spearman correlation coefficients. The equality of variances was tested using the Bartlett statistical test for samples with normal distribution and the Fligner Killen test for samples with semi-normal distribution. Multiple comparisons of parametric data were tested with post-hoc analyses using Tukey range tests (equal variances) and Tamhane's T2 (unequal variances). Multiple comparisons of non-parametric data were performed by Wilcoxon signed-rank test. Estimated study population size was 54 patients per group, with a 5% rate of study discontinuation, to detect significant changes in HOMA-IR among groups with a statistical power of 95%. Two-tailed significance was defined as $p < 0.05$. ❑

RESULTS

Baseline demographic and somatometric study groups' characteristics

The flow diagram for the study is displayed in Figure 1. During the study period, a total of 158 consecutive eligible patients were included in the study (mean age 60.18 years, 62% males). At baseline, 53 patients were randomized in the DEL/MANI group, 51 in the TEL/AMLO group and 54 in the VAL/AMLO group. There was no significant difference in age, height, body weight, body mass index (BMI), SBP and DBP among study groups prior to treatment initiation. Since no statistically significant differences in age were observed across study groups ($p > 0.1$), the application of age matching was not considered necessary for the purposes of this study. The same stands for logistic regression analysis, considering the fact that no statistically significant

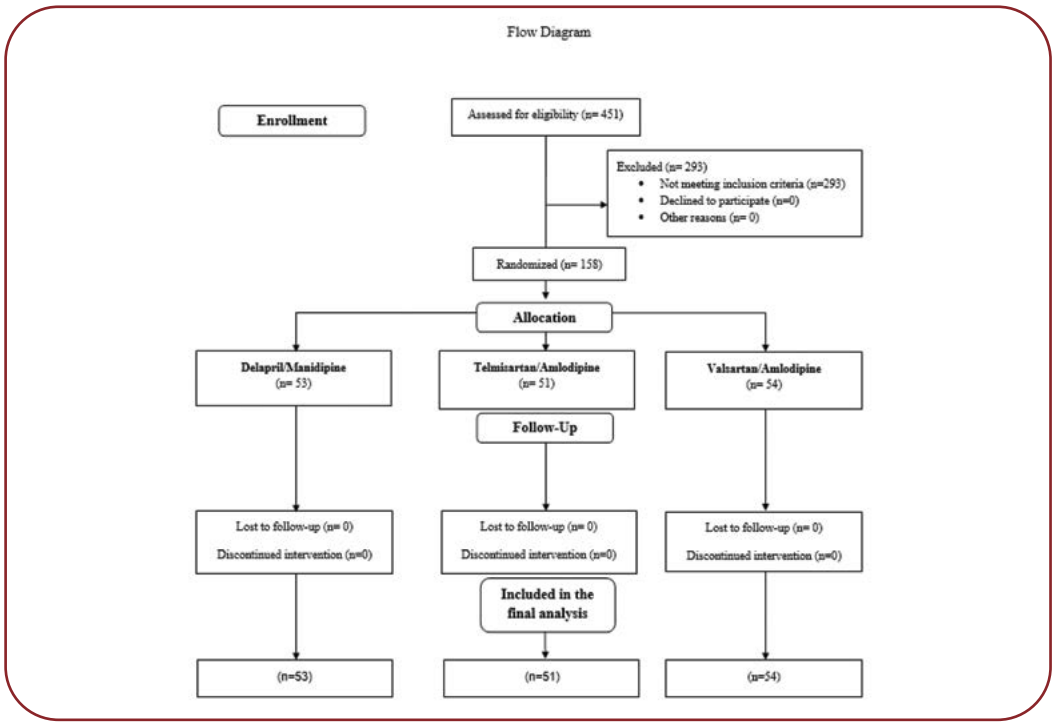

FIGURE 1. Flow diagram of the study

TABLE 1. Baseline characteristics of the study population

	DEL/MANI	TEL/AMLO	VAL/AMLO	p-value
N (men)	53 (30)	51 (35)	54 (33)	NS
Age (years)	58.1 ± 11.7	58.0 ± 13.6	64.4 ± 11.6	NS (0.872)
Smokers, n (%)	12 (22.6)	13 (25.4)	14 (25.9)	NS
Body weight (Kg)	83.7 ± 13.2	84.7 ± 12.9	80.8 ± 11.8	NS (0.732)
BMI (Kg/m^2)	28.7 [27.7-30.3]	29.3 [27.4-31.7]	28.1 [26.8-29.9]	NS (0.645)
SBP (mm Hg)	156 [151-161]	163 [158-168]	162 [159-165]	NS
DBP (mm Hg)	100 [88-101]	100 [95-106]	100 [92-104]	NS

DEL/MANI=delapril/manidipine; TEL/AMLO=telmisartan/amlodipine;
VAL/AMLO=valsartan/amlodipine; BMI=body mass index; SBP=systolic blood pressure;
DBP=diastolic blood pressure; NS=non-significant
Data are presented as percentage (size), mean value ± standard deviation, median [25th-75th].
*p < 0.05 compared to DEL/MANI treatment
^p < 0.05 compared to TEL/AMLO treatment
$ p < 0.05 compared to VAL/AMLO treatment

differences in age, gender or BMI (p > 0.1) confounders were identified. Baseline demographic characteristics of the study population are presented in Table 1.

Effect of 12-week dual antihypertensive treatment on carbohydrate metabolism and other glycemic parameters

HOMA-IR index reduced by 22.55%, in the TEL/AMLO group (p < 0.01), while no significant difference was observed in the DEL/MANI and VAL/AMLO groups after 12-week treatment (Table 2). Between groups, HOMA-IR index changes were significantly lower in the TEL/AMLO compared with DEL/MANI group (p < 0.05) and VAL/AMLO group (p < 0.001) (Figure 2 and Table 2).

Glu was significantly reduced in the DEL/MANI and TEL/AMLO groups (p < 0.01), while no statistically significant difference was observed in the VAL/AMLO group (Table 2). In addition, no significant difference was observed between all groups after 12 weeks.

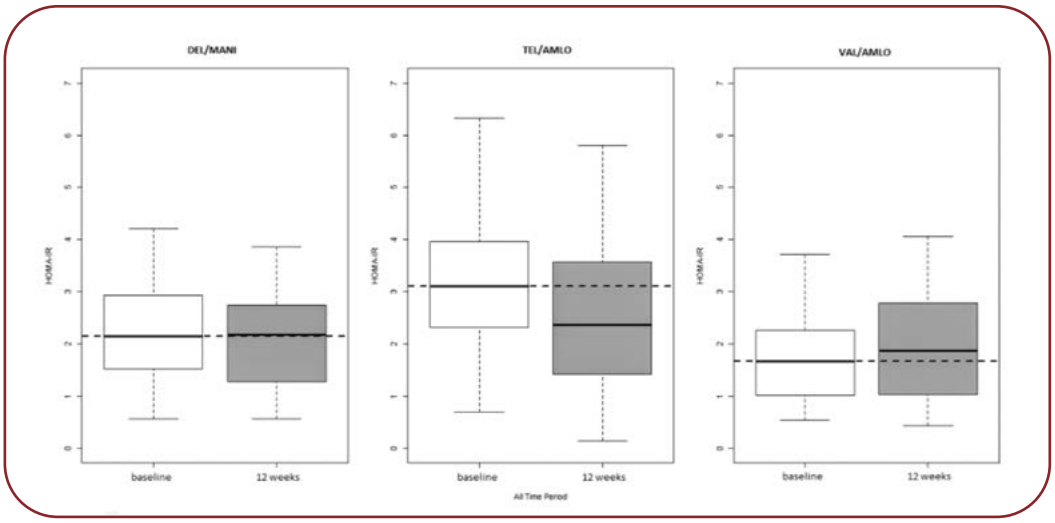

FIGURE 2. Change in HOMA-IR (DEL/MANI=delapril/manidipine; TEL/AMLO=telmisartan/amlodipine; VAL/AMLO=valsartan/amlodipine)

TABLE 2. Effects of treatment on carbohydrate metabolism parameters in each study group

Parameter	Baseline	12 weeks	% change (absolute change)	p-value
Glucose (mg/dL)				
DEL/MANI	100 [97-107]	98.45 ± 13.22	-1.55 (-1.55)	0.004
TEL/AMLO	100 [98-106]	98.22 ± 13.24	-1.78 (-1.78)	0.005
VAL/AMLO	104 [96-110]	103.96 ± 10.51	-0.04 (-0.04)	0.622
Insulin (µIU/mL)				
DEL/MANI	8.6 [6.3-11.4]	9 [5.8-11.8]	4.65 (+0.4)	0.602^^
TEL/AMLO	13 [9.5-14.9]	10 [6.2-13.5]	-23.08 (-3)	0.005**$$$
VAL/AMLO	6.2 [4.2-9.2]	7.2 [4.8-10.5]	16.13 (+1)	0.136^^^
HbA_{1C} (%)				
DEL/MANI	5.6 ± 0.55	5.64 ± 0.57	0.71 (+0.04)	0.195
TEL/AMLO	5.67 ± 0.44	5.71 ± 0.46	0.71 (+0.04)	0.497
VAL/AMLO	5.79 ± 0.33	5.75 ± 0.32	-0.69 (-0.04)	0.236
HOMA-IR				
DEL/MANI	2.14 [1.52-2.89]	2.17 [1.35-2.74]	1.4 (+0.03)	0.577^
TEL/AMLO	3.06 [2.27-3.91]	2.37 [1.44-3.61]	-22.55 (-0.69)	0.005*$$$
VAL/AMLO	1.66 [1.01-2.18]	1.87 [1.05-2.83]	12.65 (+0.21)	0.072^^^

DEL/MANI=delapril/manidipine; TEL/AMLO=telmisartan/amlodipine, VAL/AMLO=valsartan amlodipine; HOMA-IR=homeostatic model assessment for insulin resistance.

Data are presented as average ± standard deviation, median [25th-75th].

*p < 0.05 compared to DEL/MANI treatment, **p < 0.01 compared to DEL/MANI treatment, ***p < 0.001 compared to DEL/MANI treatment

^p < 0.05 compared to TEL/AMLO treatment, ^^p < 0.01 compared to TEL/AMLO treatment, ^^^p < 0.001 compared to TEL/AMLO treatment

$p < 0.05 compared to VAL/AMLO treatment, $$p < 0.01 compared to VAL/AMLO treatment, $$$p < 0.001 compared to VAL/AMLO treatment

Glu=fasting serum glucose, INS=fasting insulin, HOMA-IR=homeostatic model assessment for insulin resistance, HbA_{1c}=Hemoglobin A_{1c}

INS was significantly reduced in the TEL/AMLO group ($p < 0.01$). No significant difference was observed in the DEL/MANI and VAL/AMLO groups (Table 2). Between groups, INS was also significantly lower in the TEL/AMLO group compared with DEL/MANI and VAL/AMLO groups (all $p < 0.01$), respectively (Table 2).

Changes in BP levels and somatometric characteristics

SBP levels were significantly lowered in all groups ($p < 0.001$), with a mean change of -18 mm Hg for the DEL/MANI group, -24 mm Hg for the TEL/AMLO group, and -22 mm Hg for the VAL/AMLO group (Table 3).

DBP levels also dropped in all groups ($p < 0.001$): mean change of -1 mm Hg for the DEL/MANI group, -15 mm Hg for the TEL/AMLO group, and -13 mm Hg for the VAL/AMLO group (Table 3).

Comparisons between treatment groups showed a statistically significant difference in the change of SBP levels in the DEL/MANI group *vs.* VAL/AMLO ($p < 0.05$) and TEL/AMLO groups ($p < 0001$) (Table 3). Of note, the DEL/MANI treatment group showed the smallest decrease in SBP levels.

BMI and waist circumference had no significant change at the end of treatment for each group and between group comparisons.

TABLE 3. Changes in somatometrics and blood pressure measurements following treatment allocation

ameter	baseline	12 weeks	% change (absolute change)	p-value
ist circumference (cm)				
L/MANI	105.2 ± 9.36	105.0± 9.12	-0.2 (-0.2)	NS
L/AMLO	107.0 ± 8.33	106.9 ± 8.68	-0.09 (-0.1)	NS
L/AMLO	103.0 ± 8.81	102.9 ± 8.22	-0.1 (-0.1)	NS
I (Kg/m^2)				
L/MANI	28.7 [27.7-30.3]	28.6[27.0-30.1]	-0.3 (-0.1)	NS
L/AMLO	29.3 [27.4-31.7]	29.3 [26.7-31.8]	0 (0)	NS
L/AMLO	28.1 [26.8-29.9]	28.1 [26.3-29.7]	0 (0)	NS
P (mm Hg)				
L/MANI	156 [151-161]	138 [132-145]	-11.5 (-18)	<0.001^^^$
L/AMLO	163 [158-168]	139 [135-143]	-14.7 (-24)	<0.001
L/AMLO	162 [159-165]	140 [135-145]	-13.6 (-22)	<0.001*
P (mm Hg)				
L/MANI	100 [88-101]	88 [82-90]	-12 (-12)	<0.001
L/AMLO	100 [95-106]	85 [80-89]	-15 (-15)	<0.001
L/AMLO	100 [92-104]	87 [78-90]	-13 (-13)	<0.001

'MANI=delapril/manidipine; TEL/AMLO=telmisartan/amlodipine;
/AMLO=valsartan/amlodipine; BMI=body mass index; SBP=systolic blood pressure;
=diastolic blood pressure.
are presented as average ± standard deviation, median [25th-75th].
0.05 compared to DEL/MANI treatment, **p < 0.01 compared to DEL/MANI treatment,
< 0.001 compared to DEL/MANI treatment
0.05 compared to TEL/AMLO treatment, ^^p < 0.01 compared to TEL/AMLO treatment,
< 0.001 compared to TEL/AMLO treatment
0.05 compared to VAL/AMLO treatment, $$p < 0.01 compared to VAL/AMLO treatment,
< 0.001 compared to VAL/AMLO treatment

Tolerability and compliance

All patients completed the study protocol successfully, while no serious adverse events were reported during the study nor were there any clinically significant elevations in markers of renal function or potassium levels (data not shown). ❑

DISCUSSION

This study evaluated the effects of fixed-dose single pill combinations of RAS blockers with a CCB, namely TEL/AMLO, DEL/MANI and VAL/AMLO, on indices of glucose metabolism in patients with IFG and hypertension.

All three treatment combinations were effective in lowering both SBP and DBP. However, only the TEL/AMLO combination was associated with a significant reduction in HOMA-IR by 22%, whereas DEL/MANI and VAL/AMLO treatment were associated with an increase of this index (1.4% and 12.7%, respectively) after the 12-week treatment period.

The importance of the HOMA-IR has been documented in several studies. For example, in Women's Health Initiative (multiethnic cohort of postmenopausal women) high HOMA-IR was independently and consistently associated with an increased T2D risk (23). HOMA-IR is a useful tool to distinguish healthy individuals from those with IR and those with T2DM (24, 25). However, its cut-off values vary with age, gender and among different ethnic groups (26-28). Similar to this, its cut-off values have not been clearly defined among European populations (27, 29-31).

Regarding antihypertensive treatment, RAS blockers and CCBs are considered to minimally affect glucose metabolism. ACEi and ARBs exert

vasodilatory action and may increase skeletal muscle blood flow resulting in changes of insulin sensitivity (32). They also exert protective effects against the oxidative potential of angiotensin II and stimulate insulin secretion from pancreatic islets via potassium retention and peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist actions (32).

CCBs are generally considered to have an overall neutral metabolic profile (33). However, it has been suggested that CCBs (amlodipine in particular) may improve insulin sensitivity by exerting vasodilatory action in insulin-sensitive tissues without stimulating sympathetic nervous system by preventing the inhibition of glucose transporters and calcium mediated glycogen synthase or through antioxidant effects (32). In a meta-analysis of five clinical trials comparing ARBs and CCBs with regard to the effect on insulin resistance, ARBs reduced the HOMA-IR index (mean difference -0.65, 95% CI -0.93 to 0.38) and fasting insulin (mean difference -2.01, 95% CI -3.27 to 0.74) more than CCBs (34). Manidipine may exert a beneficial effect on insulin resistance, and this has been described both in non-diabetic and T2D patients (35, 36). This effect of manidipine has been attributed to partial activation PPAR-γ (37, 38).

Current data regarding the effect of VAL/AMLO combination and the effect on HOMA-IR are scarce. In a randomized clinical trial of 58 patients receiving amlodipine or valsartan or a combination of the two drugs, it was shown that all three treatment regimens had a favorable effect on carbohydrate metabolism, but the combined treatment was superior to monotherapies in terms of insulin sensitivity (39). This trial differs from our study in its design: the study population included patients without IFG at baseline and the evaluation of insulin sensitivity was estimated by glucose infusion rate (GIR, mg/kg/min) expressed as the amount of glucose injected during the last 30 minutes.

Another comparative study involved patients with essential AH who were randomized to either valsartan (160 mg) and amlodipine (5 mg) or valsartan (160 mg) and hydrochlorothiazide (12.5 mg) (40). A total of 60 patients completed the study (30 in the VAL/AMLO group and 30 in the valsartan/hydrochlorothiazide group). No significant changes were observed in either group of patients regarding carbohydrates metabolism (fasting serum glucose, insulin and HOMA-IR index) (40). In the VAL/AMLO group, HOMA-IR index increased by 0.1 unit from baseline [0.8 (0.4-3.0)] *vs.* at the end of treatment [0.9 (0.4-3.7)] (40).

Telmisartan is a partial PPAR-γ agonist and retains this ability even when given in low doses (33). Telmisartan has been associated with an improvement in the resistance of peripheral tissues to the action of insulin (41, 42). Of note, a meta-analysis showed that telmisartan is superior to other ARBs in improving HOMA-IR (mean difference = -0.23, 95% CI -0.40 to -0.06) (43). Data from large randomized controlled trials showed that telmisartan may either have no effect (44) or reduce the incidence of new-onset T2D (45-47).

Delapril, has favorable effects in hypertensive patients with glucose intolerance and improves insulin sensitivity (48-50). In a study comparing the effects of DEL/MANI combination treatment *vs.* olmesartan/hydrochlorothiazide on insulin sensitivity (assessed by GIR), a significant increase only with DEL/MANI combination was observed (51). However, in our study the combination of DEL/MANI was associated with an increase in HOMA-IR. Differences in study design as well as baseline characteristics of study population may hold accountable.

Our findings should be interpreted in the light of certain limitations. This was an open-label study with a relatively short period of follow-up and therefore no hard clinical endpoints were applied. However, to our knowledge, the effects of various fixed RAS blocker plus CCB combinations on insulin resistance in patients with AH and IFG have not previously addressed. No control group receiving placebo or monotherapy was included, which was decided mainly on the account of need for treatment. Finally, compliance with treatment was based on pill counts and self-report. ❑

CONCLUSIONS

In conclusion, fixed combination single pill treatment with telmisartan and amlodipine appears to have a favorable effect on insulin resistance compared with valsartan plus amlodipine as well as delapril plus manidipine in hypertensive patients with impaired fasting glucose.

Whether this action favorably affects outcomes must be further evaluated. ❑

Ethics approval and consent to participate: The study protocol was approved by the Institutional Ethics Committee of University Hospital of Ioannina and informed consent was obtained from the participant.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest: AL, DM, GA, CP, P-SA, and KB report no conflicts of interest. HM is participating in educational, research and consulting activities sponsored by healthcare companies, including Amgen, Bayer, Pfizer, Servier, Viatris. EL has personal fees from AMGEN, NOVARTIS, MYLAN, SERVIER, and CHIESI outside the submitted work. ME reports personal fees from AMGEN, NOVARTIS, MYLAN, and SERVIER. GL has personal fees from AMGEN, NOVARTIS, and MYLAN.

Financial support: none declared.

Authors' contributions: All authors equally contributed to conceptualization, study design, data collection, data analysis, data interpretation and drafted the article. All authors read and approved the final manuscript.

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