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Effect of nebivolol or nebivolol/hydrochlorothiazide plus atorvastatin on glycemic profile in patients with hypertension and dyslipidemia

Σύγκριση της επίδρασης χορήγησης νεμπιβολόλης ή νεμπιβολόλης/υδροχλωροθειαζίδης μαζί με ατορβαστατίνη στο γλυκαιμικό προφίλ ασθενών με αρτηριακή υπέρταση και δυσλιπιδαιμία

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AIM: A potentially diabetogenic role for statins has been suggested. Similarly, first and second generation beta-blockers and hydrochlorothiazide (HCTZ) have negative effects on glucose homeostasis. Nebivolol is a third generation beta-blocker which may beneficially affect carbohydrate metabolism. The effect of combined treatment with nebivolol, HCTZ and atorvastatin is unknown.
MATERIAL-METHODS: This is a prospective, randomized, open-label, blinded endpoint (PROBE) study. Drug-naive patients with hypertension and dyslipidemia were recruited. All patients received atorvastatin (10 mg). In addition, patients with stage 1 hypertension received nebivolol (5 mg, AN group), while patients with stage 2 hypertension received nebivolol/HCTZ (5/12.5 mg, AN/H-12.5 group or 5/25 mg, AN/H-25 group).

ΣΚΟΠΟΣ: Τελευταία γίνεται μεγάλη συζήτηση σχετικά με την αρνητική επίδραση που ενδεχομένως ασκούν οι στατίνες και τα αντιυπερτασικά φάρμακα στην ομοιοστασία των υδατανθράκων. Συγκεκριμένα, τόσο η ατορβαστατίνη όσο και τα θειαζιδικά διουρητικά και οι β-αποκλειστές ασκούν δυσμενή επίδραση στο γλυκαιμικό προφίλ. Η νεμπιβολόλη, σε αντίθεση με τους κλασικούς β-αποκλειστές, έχει συσχετισθεί με βελτίωση της ομοιοστασίας των υδατανθράκων. Ωστόσο, η επίδραση της συγχορήγησης ατορβαστατίνης-νεμπιβολόλης με ή χωρίς υδροχλωροθειαζίδη στον μεταβολισμό των υδατανθράκων παραμένει άγνωστη.
ΥΛΙΚΟ-ΜΕΘΟΔΟΣ: Στρατολογήθηκαν ασθενείς με αρτηριακή υπέρταση και δυσλιπιδαιμία που δεν είχαν λάβει καμία αντιυπερτασική ή υπολιπιδαιμική αγωγή

Η παρούσα μελέτη πραγματοποιήθηκε με υποτροφία από την Ελληνική Εταιρεία Μελέτης της Υπέρτασης

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The primary efficacy endpoint was the between group mean change from baseline in homeostasis model assessment of insulin resistance (HOMA-IR) index at 12 weeks. **RESULTS**: Seventy-eight patients completed the study. In both AN and AN/H-12.5 group HOMA-IR levels did not significantly change [from 1.6 (1.4–2.1) to 1.5 (1.4–2.0, P=NS) compared with baseline and from 1.6 (1.3–2.2) to 1.7 (1.7–2.4), P=0.07 compared with baseline), respectively]. In contrast, the HOMA-IR significantly increased by 10% in the AN/H-25 group [from 1.7 (1.3–2.3) to 1.9 (1.4–2.4), P=0.02 compared with baseline and P<0.01 for the comparison with the other 2 groups]. **CONCLUSIONS**: Administration of nebivolol may counterbalance the negative effects on HOMA-IR of atorvastatin with or without HCTZ 12.5 mg but not that of atorvastatin plus HCTZ 25 mg.

Key words: Atorvastatin, glucose, HOMA-IR, insulin, nebivolol, hydrochlorothiazide.

για τουλάχιστον 6 εβδομάδες πριν από τη συμμετοχή τους στη μελέτη. Όλοι οι συμμετέχοντες έλαβαν ατορβαστατίνη (10 mg) και επιπρόσθετα οι ασθενείς με υπέρταση σταδίου 1 έλαβαν νεμπιβολόλη (5 mg, ομάδα AN), ενώ οι ασθενείς με υπέρταση σταδίου 2 έλαβαν συνδυασμό νεμπιβολόλης/υδροχλωροθειαζίδης (5/12,5 mg, ομάδα AN/Y-12,5 ή 5/25 mg, ομάδα AN/Y-25). Το πρωτογενές καταληκτικό σημείο ήταν η μεταβολή του δείκτη αντίστασης στην ινσουλίνη HOMA-IR 3 μήνες μετά την έναρξη της θεραπείας. **ΑΠΟΤΕΛΕΣΜΑΤΑ**: Εβδομήντα οκτώ ασθενείς ολοκλήρωσαν τη μελέτη. Τόσο στην ομάδα AN όσο και στην ομάδα AN/Y-12,5 δεν παρατηρήθηκε σημαντική μεταβολή των επιπέδων του HOMA-IR [από 1,6 (1,4–2,1) σε 1,5 (1,4–2,0) και από 1,6 (1,3–2,2) σε 1,7 (1,7–2,4), αντίστοιχα, P=NS σε σύγκριση με τα αρχικά επίπεδα], ενώ στην ομάδα AN/Y-25 που παρατηρήθηκε αύξηση κατά 10% [από 1,7 (1,3–2,3) σε 1,9 (1,4–2,4), P=0,02 σε σύγκριση με τα αρχικά επίπεδα και P<0,01 για όλες τις συγκρίσεις μεταξύ των ομάδων]. **ΣΥΜΠΕΡΑΣΜΑΤΑ**: Η χορήγηση νεμπιβολόλης φαίνεται να αντιρροπεί τη δυσμενή επίδραση της ατορβαστατίνης με ή χωρίς 12,5 mg υδροχλωροθειαζίδης στα επίπεδα του HOMA-IR αλλά όχι και της ατορβαστατίνης με 25 mg υδροχλωροθειαζίδης.

Λέξεις ευρετηρίου: Ατορβαστατίνη, γλυκόζη, HOMA-IR, ινσουλίνη, νεμπιβολόλη, υδροχλωροθειαζίδη.

1. Introduction

Diabetes is a worldwide health problem with epidemic proportions which may lead to functional disability, vascular complications and premature death. Thus, the prevention or delay of diabetes development is of major clinical importance.[1,2] Hypertension is considered as a risk factor for new onset diabetes and hypertensive patients usually receive a statin in addition to antihypertensive drugs.[3] However, a possible diabetogenic role for statins has been suggested both from large trials and meta-analyses.[4] Several statins have been shown to increase insulin resistance indices, glucose levels and glycosylated hemoglobin (HbA1c).[5,6] Moreover, both first and second generation beta-blockers and hydrochlorothiazide (HCTZ), the most commonly used diuretic, have been associated with negative effects on glucose profile.[7,8] The combination of a beta-blocker plus HCTZ is associated with the most pronounced increase in new diabetes.[9] On the contrary, nebivolol, a third generation b1 selective beta-blocker, has been associated with a beneficial effect on glucose metabolism and may ameliorate the negative effect of HCTZ in hypertensive patients.[10] The possible effects of combined treatment with atorvastatin plus nebivolol with or without HCTZ on carbohydrate metabolism remain unknown.

The aim of the present study was to evaluate the effect of nebivolol or nebivolol/HCTZ plus atorvastatin on glycemic profile in patients with hypertension and dyslipidemia. The primary endpoint was the between group difference in mean change from baseline in HOMA-IR index at 12 weeks.

2. Patients-method

This was a prospective, randomized, open-label, blinded endpoint (PROBE) study. Consecutive subjects with dyslipidemia and hypertension attending the Outpatient Lipid and Obesity Clinic of the University Hospital of Ioannina, Ioannina, Greece were recruited.

Eligible patients were hypertensive drug-naive subjects with low density lipoprotein cholesterol (LDL-C) levels above those recommended by the European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS) based on each patient risk score.[11] Diagnosis of hypertension was based on abnormally high blood pressure (BP) measurements of ≥2 properly measured, seated blood pressure (BP) readings on each of 2 or more outpatient visits.

Subjects with: (i) history of ischemic heart disease or any other vascular disease, (ii) impaired hepatic function [aspartate and/alanine aminotransferase (AST and/or ALT) >2x the upper normal limit and/or history of chronic liver disease, such as cirrhosis], (iii) alcohol abuse, (iv) impaired renal function (serum creatinine >1.6 mg/dL), (v) diabetes [present if a subject was treated for diabetes or by 2 separate fasting plasma glucose (FPG) measurements ≥126 mg/dL], (vi) severe hypertriglyceridemia [triglyceride (TG) levels >500 mg/dL], (vii) thyroid dysfunction [thyroid stimulating hormone (TSH) levels >5.0 μU/L], and (viii) patients who received hypolipidemic or antihypertensive drugs in the last 3 months prior to recruitment were excluded.

All patients were given atorvastatin 10 mg/day. In addition, patients with stage 1 hypertension were prescribed nebivolol 5 mg/day (AN group), while patients with stage 2 hypertension were randomized to fixed combination of nebivolol 5 mg/day plus HCTZ 12.5 mg/day (AN-H/12.5 group) or nebivolol 5 mg/day plus HCTZ 25 mg/day (AN-H/25).

The primary endpoint was the between group difference in mean change from baseline in HOMA-IR index at 12 weeks. Secondary efficacy endpoints included changes in FPG and HbA1c levels, blood pressure, heart rate and lipid profile.

All patients were given similar dietary advice. Compliance with treatment and lifestyle habits was assessed by questionnaire and tablet count. All study participants gave their written informed consent prior to enrolment, and the Ethics Committee of the University Hospital of Ioannina approved the study protocol.

3. Laboratory measurements

Visits took place at baseline and 12 weeks after the start of treatment. At each visit, BP was measured in triplicate in the right arm after patients had rested for 10 minutes in a sitting position. Measurements were performed by trained clinicians using an electronic sphygmomanometer (WatchBP Office, Microlife WatchBP AG,Widnau, Switzerland). Blood samples for laboratory tests were obtained after a 12 h overnight fast. Serum levels of FPG, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and TG were determined enzymatically in the laboratory of the University Hospital of Ioannina using an Olympus AU 600 analyzer (Olympus Diagnostica GmbH, Hamburg, Germany). Intra-assay and total coefficient variations for glucose assay were 0.7% and 1.6%, respectively. LDL-C was calculated using the Friedewald equation [provided that TGs were <350 mg/dL (3.95 mmol/L)]. The determination of HbA1c (expressed as percentage of the total hemoglobin concentration) was based on a latex agglutination inhibition assay (Randox Laboratories Ltd., Crumlin, United Kingdom). HbA1c values are expressed as percentage of the total hemoglobin concentration. The sensitivity of the assay is 0.25 g/dL of HbA1c and the within -and between-run precision is <6.67% and <4.82%, respectively. Fasting serum insulin was measured by an AxSYM insulin assay microparticle enzyme immunoassay on an AzSYM analyzer (Abbott Diagnostics, Illinois, United States). Intra-assay and total coefficient variations for insulin assay were 4.1% and 5.3%, respectively. The HOMA-IR index was calculated as follows: HOMA-IR index=fasting insulin (mU/L)×FPG (mg/dL)/405. All laboratory determinations were performed blindly with regard to treatment allocation.

4. Statistics

We calculated that a sample size of 75 will give a 90% power to detect a significant difference in HOMA-IR change between groups. Values are given as mean±SD and median (range) for parametric and non-parametric data, respectively. Continuous variables were tested for lack of normality by the Kolmogorov-Smirnov test, and logarithmic transformations were accordingly performed for nonparametric variables. The paired-sample t-test was used for assessing the effect of treatment in each group. Analysis of covariance (ANCOVA), adjusted for baseline values, was used for comparisons between groups. All reported p values are based on two-sided tests with a significance level of 0.05. Analyses were performed using the Statistical Package for the SPSS 15.0 (SPSS Inc, Chicago, IL).

5. Results

Recruitment took place from September 2012 to October 2013 and follow up ended in January 2014. Seventy-eight (42 men, 59±11 years) patients were enrolled and completed the study (n=32, 26 and 20 in the AN, AN/H-12.5 and AN/H-25 group, respectively). Except for BP values, no significant differences in baseline data were found across groups regarding demographic characteristics and serum metabolic parameters (table 1). Compliance rate was >80% in all participants. No changes in body weight, dietary habits (including salt intake), or medications were reported during the follow up.

6. Effect on glycemic profile

In both AN and AN/H-12.5 group HOMA-IR levels did not significantly change, while in the AN/H-25 HOMA-IR increased by 10% (P=0.02 compared with baseline and P<0.01 for comparisons with the other 2 groups). FPG levels did not significantly change in the AN group and in the AN/H-12.5 group, while they increased by 7% in the AN/H-25 group (P=0.01 compared with baseline and P<0.01 for comparisons with the other 2 groups). Both AN and AN/H-12.5 groups were not associated with significant changes in HbA1c levels, while in the AN/H-25 group HbA1c levels increased by 0.3% (P=0.03 compared with baseline and P=0.01 compared with the other 2 groups) (table 2).

7. Effect on lipid profile

Total cholesterol and LDL-C levels decreased similarly in all treatment groups (P<0.01 compared with baseline in all groups). Triglyceride and HDL-C levels did not significantly change in any group (table 3).

8. Effect on BP levels and heart rate

Systolic BP decreased by 7 mmHg in the AN group (P<0.01 compared with baseline), while a greater reduction was reported in the AN/H-12.5 and AN/H-25 groups (by 11 and 12 mmHg, respectively, P<0.01 compared with baseline). Diastolic BP decreased by 7, 10 and 12 mmHg in the AN, AN/H-12.5 and AN/H-25 groups, respectively (P<0.01 compared with baseline). Heart rate decreased similarly in all treatment groups (by 6%, 5% and 5% in the AN, AN/H-12.5 and AN/H-25, respectively, P<0.01 compared with baseline) (table 3).

9. Discussion

To our best of knowledge this is the first study evaluating the effect of combined administration of a statin plus beta blocker with or without a diuretic on

Table 1. Baseline characteristics of patients who completed the study* (N = 78)

	AN	AN/H-12.5	AN/H-25	P
N (males/females)	32 (17/15)	26 (14/12)	20 (11/9)	NS
Age, years	61±10	58±14	59±12	NS
SBP, mmHg	148±5	165±5	167±5	0.01
DBP, mmHg	96±3	103±3	105±4	0.01
HR, bpm	80±4	79±5	82±3	NS
Metabolic syndrome (%)	17 (53)	15 (58)	11 (55)	NS
Smoking (%)	10 (31)	9 (35)	7 (35)	NS
HOMA-IR	1.6 (1.4–2.1)	1.6 (1.3–2.2)	1.7 (1.3–2.3)	NS
FPG, mg/dL (mmol/L)	94±7 (5.2±0.4)	95±7 (5.3±0.4)	94±6 (5.2±0.3)	NS
HbA1c (%)	5.4±0.5	5.5±0.4	5.3±0.5	NS
BMI, kg/m^2	29.1±2.5	29.1±3.1	28.8±3.2	NS
TC, mg/dL (mmol/L)	224±22 (5.8±0.6)	220±17 (5.7±0.4)	225±21 (5.8±0.5)	NS
Triglycerides, mg/dL [mmol/L]	117 (89–159) [1.3 (1.0–1.8)]	123 (88–160) [1.4 (0.9–1.8)]	118 (90–150) [1.3 (1.0–1.7)]	NS
HDL-C, mg/dL (mmol/L)	48±5 (1.2±0.1)	49±7 (1.3±0.2)	47±6 (1.2±0.2)	NS
LDL-C, mg/dL (mmol/L)	153±12 (3.9±0.3)	146±15 (3.8±0.4)	154±14 (3.9±0.4)	NS

AN: atorvastatin-nebivolol group, *AN/H-12.5*: atorvastatin-nebivolol-hydrochlorothiazide 12.5 mg group, *AN/H-25*: atorvastatin-nebivolol-hydrochlorothiazide 25 mg group, NS: non-significant, BMI: body mass index, *HOMA-IR*: homeostasis model assessment of insulin resistance index, *FPG*: fasting plasma glucose, *HbA1c*: glycosylated hemoglobin, *TC*: total cholesterol, *HDL-C*: high-density lipoprotein cholesterol, *LDL-C*: low-density lipoprotein cholesterol, *SBP*: systolic blood pressure, *DBP*: diastolic blood pressure, *HR*: heart rate
*Values are expressed as mean ± standard deviation [except for triglycerides which are expressed as median (range)]

Table 2. Glycemic profile at baseline and 3 months after treatment.*

	Baseline	3 months	Percentage change (%)
HOMA-IR			
AN	1.6 (1.4–2.1)	1.5 (1.4–2.0)	–6
AN/H-12.5	1.6 (1.3–2.2)	1.7 (1.7–2.4)	+6
AN/H-25	1.7 (1.3–2.3)	1.9 (1.4–2.4)	+10[i–iii]
FPG, mg/dL (mmol/L)			
AN	94±7 (5.2±0.4)	95±6 (5.3±0.3)	+1
AN/H-12.5	95±7 (5.3±0.4)	99±7 (5.5±0.4)	+4
AN/H-25	94±6 (5.2±0.3)	101±7 (5.6±0.4)	+7[i–iii]
HbA1c (%)			
AN	5.4±0.5	5.5±0.4	+0.1
AN/H-12.5	5.5±0.4	5.6±0.3	+0.1
AN/H-25	5.3±0.5	5.6±0.4	+0.3[i–iii]

HOMA-IR: homeostasis model assessment of insulin resistance index, *FPG*: fasting plasma glucose, *AN*: atorvastatin-nebivolol group, *AN/H-12.5*: atorvastatin-nebivolol-hydrochlorothiazide 12.5 mg group, *AN/H-25*: atorvastatin-nebivolol-hydrochlorothiazide 25 mg group, *HbA1c*: glycosylated hemoglobin

*Values are expressed as mean ± standard deviation [except for HOMA-IR index which is expressed as median (range)]

(i) p<0.05 versus baseline, (ii) p<0.05 versus AN, (iii) p <0.05 versus AN/H-12.5 group

Table 3. Lipid profile, blood pressure and heart rate at baseline and 3 months after treatment.*

	Baseline value	3 months	change (%)
TC, mg/L (mmol/L)			
AN	224±22 (5.8±0.6)	160±15 (4.1±0.4)	–29[i]
AN/H-12.5	220±17 (5.7±0.4)	162±18 (4.2±0.5)	–26[i]
AN/H-25	225±21 (5.8±0.5)	160±19 (4.1±0.5)	–29[i]
Triglycerides, mg/L [mmol/L]			
AN	117 (89–159) [1.3 (1.0–1.8)]	107 (83–148) [1.2 (0.9–1.7)]	–9
AN/H-12.5	123 (88–160) [1.4 (0.9–1.8)]	115 (80–150) [1.30 (0.9–1.7)]	–7
AN/H-25	118 (90–150) [1.3 (1.0–1.7)]	110 (85–145) [1.2 (1.0–1.6)]	–7
HDL-C, mg/L (mmol/L)			
AN	48±5 (1.2±0.1)	50±6 (1.3±0.2)	+4
AN/H-12.5	49±7 (1.3±0.2)	50±4 (1.3±0.1)	+2
AN/H-25	47±6 (1.2±0.2)	46±5 (1.2±0.1)	–2
LDL-C, mg/L (mmol/L)			
AN	153±12 (3.9±0.3)	95±13 (2.5±0.3)	–38[i]
AN/H-12.5	146±15 (3.8±0.4)	89±14 (2.3±0.4)	–39[i]
AN/H-25	154±14 (3.9±0.4)	92±15 (2.4±0.4)	–40[i]
SBP, mmHg			
AN	148±5	138±6	–7[i]
AN/H-12.5	165±5	149±5	–11[i,ii]
AN/H-25	167±5	147±7	–12[i,ii]
DBP, mmHg			
AN	96±3	89±4	–7[i]
AN/H-12.5	103±3	93±3	–10[i,ii]
AN/H-25	105±4	92±5	–12[i,ii]
HR, bpm			
AN	80±4	75±3	–6[i]
AN/H-12.5	79±5	75±4	–5[i]
AN/H-25	82±3	78±4	–5[i]

TC: total cholesterol, *AN*: atorvastatin-nebivolol group, *AN/H-12.5*: atorvastatin-nebivolol-hydrochlorothiazide 12.5 mg group, *AN/H-25*: atorvastatin-nebivolol-hydrochlorothiazide 25 mg group, *HDL-C*: high-density lipoprotein cholesterol, *LDL-C*: low-density lipoprotein cholesterol, *SBP*: systolic blood pressure, *DBP*: diastolic blood pressure, HR: heart rate

*Values are expressed as mean±standard deviation [except for triglycerides which are expressed as median (range)].

(i) P<0.05 versus baseline, (ii) P<0.05 versus AN

glycemic profile in patients with dyslipidemia and hypertension. Both AN and AN/H-12.5 groups were not associated with significant HOMA-IR index change, while HOMA-IR significantly increased in AN/H-25 group. Similarly, HbA1c and FPG level increased in AN/H-25 group, while it did not change in the other 2 treatment groups.

In the reanalysis of data from Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial diuretics and statins were associated with increased risk of new onset diabetes, whereas the effect beta-blockers was non-significant in patients with impaired glucose tolerance and other cardiovascular risk factors.[12] Atorvastatin has been associated with increased insulin resistance, HOMA-IR index and HbA1c levels in both diabetic and non-diabetic patients.[13–15] Similarly, HCTZ has been associated with negative effects on glycemic profile.[8] Contrary to the first and second generation beta-blockers, nebivolol has been associated with beneficial effects on glucose metabolism in a number of studies.[16–19] In a previous study nebivolol (5 mg/day) lacked detrimental metabolic effect, while metoprolol (100 mg/day) decreased insulin sensitivity in patients with metabolic syndrome.[16] In another study, nebivolol (5 mg/day), in contrast to metoprolol (100 mg/day), improved oxidative stress and insulin sensitivity in hypertensive patients.[18] In hypertensive patients with impaired glucose tolerance insulin sensitivity was not modified by nebivolol (2.5–5 mg/day), while atenolol (50–100 mg/day) reduced insulin sensitivity.[17] In another study, hypertensive patients first received nebivolol and after 1 month, in those patients whose BP was not normalized HCTZ was added.[10] Nebivolol (5 mg/day) reduced HOMA-IR index but the adjunct of HCTZ (both at 12.5 and 25 mg/day) blunted this reduction.[10]

Nebivolol has been shown to increase the bioavailability of endogenous nitric oxide (NO).[19] As NO improves insulin sensitivity and muscle glucose uptake, this may contribute to the favorable effect of nebivolol on insulin sensitivity.[20] Moreover, nebivolol has been associated with increased adiponectin levels in hypertensive patients.[18] Of note, adiponectin has been associated with novel insulin-sensitizing properties.[21] The mechanism traditionally associated with this increased risk of diuretic-associated diabetes mellitus is a reduction in serum potassium. A meta-analysis of 59 studies found a significant correlation between the degree of diuretic-induced hypokalemia and an increase in plasma glucose.[22] Moreover, there is evidence that prevention of hypokalemia with potassium supplementation or potassium-sparing agents lessens the degree to which FPG is increased.[22] The mechanisms by which statins may adversely affect glucose homeostasis are not fully understood. Statins by inhibiting mevalonate pathway block the synthesis not only of cholesterol, but also of several mevalonate products known as isoprenoids.[4] Isoprenoids, including farsenyl pyrophosphate, geranylgeranyl pyrophosphate and ubiquinone, are known to enhance glucose uptake by upregulating the membrane transporter protein glucose transporter 4, which plays a key role in glucose uptake by adipocytes.[4] Therefore, statin-induced inhibition of isoprenoid synthesis may increase insulin resistance in the adipose tissue and induce hyperinsulinemia. Most potent statins in terms of inhibiting mevalonate pathway, such as atorvastatin, as well as higher doses of statin treatment may exert a more profound impact on insulin resistance compared with conventional statins at low dosage regimens. Last, statins may exert a deleterious effect on insulin secretion by pancreatic islets.[4]

As in treated hypertensive subjects, the occurrence of new diabetes portends a risk for subsequent cardiovascular disease similar to that of previously known diabetes, the raising critical question is whether our study's results translate into reduced new-onset diabetes and cardiovascular disease incidence.[23] Insulin resistance, HOMA-IR and FPG levels are independent predictors of incident diabetes.[24] Moreover, in both non diabetic and diabetic subjects, HOMA-IR index is an independent predictor of cardiovascular disease.[25–26] Thus, insulin resistance might be regarded as an accomplice in the pathogenesis of cardiovascular disease. Nevertheless, it is interesting to establish whether HOMA-IR reduction decreases cardiovascular disease risk. This information would be of great clinical value, because it might strongly justify and encourage the use of drugs capable of improving insulin sensitivity, such as nebivolol, with the aim of reducing cardiovascular risk. In this context, it is important to remember that physical activity, which improves insulin sensitivity, was shown to prevent cardiovascular disease in patients with type 2 diabetes.[27] Moreover, administration of metformin, a drug that effectively reduces HOMA-IR index, was the only therapeutic approach associated with reduced incidence of myocardial infarction in the UK Prospective Diabetes Study.[28] Specifically designed studies should address the treat-

ment-induced HOMA-IR index modulation in terms of cardiovascular risk.

It has to be underlined that the BP lowering effects of both add-on 12.5 and 25 mg of HCTZ were almost identical, but only the higher dose adversely affected glucose metabolism compared with nebivolol monotherapy. Thus, as it is stated in the recent guidelines, the administration of 12.5 mg of HCTZ may be recommended.[3] What is more, contrary to previous studies, the addition of HCTZ did not adversely affect lipid profile, regardless of the dose.[8]

10. Study limitations and strengths

A major limitation of our study is the open-label design and the lack of monotherapy groups. However, it was considered unethical to leave these high-risk patients without combined antihypertensive and hypolipidemic treatment.

On the other hand, it was an adequately powered randomized study with all laboratory determinations being performed blindly to treatment allocation. Also, study design is relevant to everyday clinical practice.

11. Conclusions

Administration of nebivolol may ameliorate the possible negative effects of atorvastatin with or without HCTZ 12.5 mg but not that of atorvastatin plus dose of HCTZ 25 mg on glucose metabolism.

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