

Clinical Study

Add-on-Statin Extended Release Nicotinic Acid/Laropiprant but Not the Switch to High-Dose Rosuvastatin Lowers Blood Pressure: An Open-Label Randomized Study

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Introduction. Nicotinic acid (NA) and statins have been associated with reductions in blood pressure (BP). **Patients and Methods.** We recruited 68 normotensive and hypertensive dyslipidemic patients who were treated with a conventional statin dose and had not achieved lipid targets. Patients were randomized to switch to high-dose rosuvastatin (40 mg/day) or to add-on current statin treatment with extended release (ER) NA/laropiprant (1000/20 mg/day for the first 4 weeks followed by 2000/40 mg/day for the next 8 weeks) for 3 months. **Results.** Switching to rosuvastatin 40 mg/day was not associated with significant BP alterations. In contrast, the addition of ER-NA/laropiprant to current statin treatment resulted in a 7% reduction of systolic BP (from 134 ± 12 to 125 ± 10 mmHg, $P < .001$ versus baseline and $P = .01$ versus rosuvastatin group) and a 5% reduction of diastolic BP (from 81 ± 9 to 77 ± 6 mmHg, $P = .009$ versus baseline and $P = .01$ versus rosuvastatin group). These reductions were significant only in the subgroup of hypertensives and were independent of the hypolipidemic effects of ER-NA/laropiprant. **Conclusions.** Contrary to the switch to high-dose rosuvastatin, the addition of ER-NA/laropiprant to statin treatment was associated with significant reductions in both systolic and diastolic BP.

1. Introduction

Hypertension and dyslipidemia, two powerful risk factors for cardiovascular disease, often coexist, and their combined effect is much greater than the sum of their individual effects [1]. Moreover, a growing body of evidence supports that dyslipidemia may predate the onset of hypertension, while a genetic link between dyslipidemia and hypertension cannot be excluded [2, 3]. Statins, the mainstay of lipid-lowering therapy, result in a significant clinical benefit both in primary and secondary cardiovascular prevention [4]. In addition to their hypolipidemic capacity, other properties may contribute to statin-induced benefits, including a reduction of blood pressure (BP) [5–9]. In this context, rosuvastatin has been associated with reductions in BP and BP variability in animal studies [6, 10].

Nicotinic acid (NA) comprises the oldest hypolipidemic drug in use since 1955, and it has been associated with BP decrease in a number of studies [11, 12]. Recently, the European Medicine Agency approved a fixed combination of extended release (ER) NA with laropiprant (a prostaglandin D2 receptor antagonist) which reduces NA-induced flushing without altering the beneficial effects of NA on lipid profile or BP [13–15].

We aimed to compare the possible BP effects of switching to high-dose rosuvastatin with add-on-current statin ER-NA/laropiprant in normotensive and hypertensive patients with primary dyslipidemia who were currently treated with a conventional statin regimen but had not achieved the treatment goals. To our best of knowledge, such comparison has not been made before. Secondary endpoints included changes in lipid profile.

2. Patients and Methods

2.1. Study Population. Consecutive subjects with primary hypercholesterolemia ($n = 70$) attending the Outpatient Lipid and Obesity Clinic of the University Hospital of Ioannina, Ioannina, Greece were recruited. Eligible patients were those treated for at least 3 months with a conventional statin dose (10–40 mg simvastatin or 10–20 mg atorvastatin or 5–20 mg rosuvastatin) and their low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C) levels were above those recommended by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP) III based on each patient risk factors [16].

Subjects with triglycerides (TG) $>500 \text{ mg/dL}$ (5.65 mmol/L), renal disease (serum creatinine levels $>1.6 \text{ mg/dL}$, $141 \mu\text{mol/L}$), hypothyroidism (thyroid stimulating hormone (TSH) $>5 \text{ IU/mL}$), and liver disease (alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >3 -fold upper limit of normal in 2 consecutive measurements) were excluded from the study. Patients with hypertension and/or diabetes were considered eligible if they were on stable medication for at least 3 months and their BP and/or glycemic profile were adequately controlled (no change in their treatment was allowed during study period).

Patients were randomly allocated (without a washout phase) to open-label high-dose rosuvastatin (40 mg/day) or to add-on current statin treatment with ER-NA/laropiprant (1000/20 mg/day for the first 4 weeks, followed by 2000/40 mg/day for the next 8 weeks) for a total of 3 months.

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.

2.2. 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. Levels of total cholesterol (TC), HDL-C, and triglycerides (TG) were determined enzymatically in the laboratory of the University Hospital of Ioannina using an Olympus AU 600 analyzer (Olympus Diagnostica GmbH, Hamburg, Germany). LDL-C was calculated using the Friedewald equation (provided that TGs were $<350 \text{ mg/dL}$ (3.95 mmol/L)). All laboratory determinations were performed blindly with regard to treatment allocation.

2.3. Statistical Analysis. We used G*Power 3.0.10 to calculate sample size. Based on previous studies we estimated that ER-NA/laropiprant would result in a 3% reduction of BP [15], while switching to rosuvastatin would not alter BP

since patients were already receiving a statin. Power analysis revealed that a sample size of 30 patients per group would give a 99% power to detect differences between groups at an α level lower than 0.05. We recruited 68 patients allowing for a dropout rate of ~10%. The Kolmogorov-Smirnov test was used to evaluate whether each parameter followed a Gaussian distribution, and logarithmic transformations were accordingly performed. Values are given as mean \pm standard deviation (SD) and median (range) for parametric and nonparametric data, respectively. The differences of study parameters between baseline and posttreatment values were evaluated by paired sample *t*-test (or Wilcoxon's rank test for non-Gaussian variables). Analysis of covariance (ANCOVA) adjusted for baseline values was used for the comparisons between treatment groups. Statistical significance was set at $P < .05$. Analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

3. Results

Recruitment took place from October 2009 to September 2010, and followup ended in December 2010. Initially, 68 Caucasian patients were enrolled. Sixty patients (27 men, 59 ± 11 years) completed the study, since 7 participants in the ER-NA/laropiprant group dropped out due to flushing as well as 1 patient in the rosuvastatin group due to ALT elevation >3 -fold upper normal limit. No cases of hypotension were reported. No difference in baseline parameters was found between the 2 groups (Table 1). Compliance rate was $>80\%$ in all participants who completed the study. No changes in body weight, dietary habits (including salt intake), or antihypertensive or antidiabetic medications were reported during the followup.

In the switch-to-rosuvastatin 40 mg/day group, no significant BP alterations were reported (Table 2). In contrast, the addition of ER-NA/laropiprant to current statin treatment resulted in a significant 7% reduction of systolic BP ($P < .001$ versus baseline and $P = .01$ versus rosuvastatin 40 mg) and a significant 5% reduction of diastolic BP ($P = .009$ versus baseline and $P = .01$ versus rosuvastatin 40 mg) (Table 2).

In the subgroup of hypertensive subjects ($n = 18$) the add-on-current-statin ER-NA/laropiprant was associated with a 7% and 6% significant reduction of systolic and diastolic BP, respectively, compared with baseline (systolic BP from 133 ± 6 to $124 \pm 11 \text{ mmHg}$, $P = .009$ and diastolic BP from 80 ± 9 to $75 \pm 6 \text{ mmHg}$, $P = .03$). In normotensive subjects ($n = 12$) the add-on-current-statin ER-NA/laropiprant resulted in similar though not significant BP alterations (-6% (from 131 ± 5 to $125 \pm 6 \text{ mmHg}$) and -5% (from 83 ± 5 to $79 \pm 6 \text{ mmHg}$), respectively, $P = \text{NS}$ versus baseline and $P = \text{NS}$ versus hypertensive subgroup). In the switch-to-rosuvastatin 40 mg group, both hypertensive and normotensive subjects demonstrated no significant BP alterations (data not shown).

Both the switch to rosuvastatin 40 mg and add-on-statin ER-NA/laropiprant significantly decreased TC, LDL-C, TGs and non-HDL-C compared with baseline (all $P < .001$) (Table 2). The change in LDL-C was more pronounced in

TABLE 1: Baseline characteristics and medications of study participants* ($n = 60$).

	Switch-to-rosuvastatin 40 mg	Add-on-statin ER-NA/laropiprant	P
N (females/males)	30 (17/13)	30 (16/14)	NS
Age (years)	62 ± 10	58 ± 14	NS
Current smokers (%)	7 (23)	10 (33)	NS
Diabetes mellitus (%)	4 (13)	6 (20)	NS
Metabolic syndrome (%)	15 (50)	16 (53)	NS
Body weight (kg)	79 ± 10	81 ± 10	NS
BMI (kg/m ²)	29.1 ± 2.5	29.1 ± 3.1	NS
Waist circumference (cm)	102 ± 8	99 ± 8	NS
SBP (mmHg)	127 ± 14	134 ± 12	NS
DBP (mmHg)	80 ± 7	81 ± 9	NS
Hypertensive subjects (%)	15 (50)	18 (60)	NS
TC (mg/dL) (mmol/L)	226 ± 36 5.8 ± 0.9	202 ± 42 5.2 ± 1.1	NS
Triglycerides (mg/dL) (mmol/L)	169 (150–189) 1.9 (1.7–2.1)	164 (141–187) 1.9 (1.6–2.1)	NS
HDL-C (mg/dL) (mmol/L)	55 ± 9 1.4 ± 0.2	47 ± 11 1.2 ± 0.3	NS
LDL-C (mg/dL) (mmol/L)	142 ± 45 3.7 ± 1.2	112 ± 35 2.9 ± 0.9	NS
Non-HDL-C (mg/dL) (mmol/L)	175 ± 33 4.5 ± 0.9	155 ± 37 4.0 ± 1	NS
Medications at baseline			
Aspirin	9	8	NS
Beta blockers	8	8	NS
HCTZ	10	11	NS
ACEIs/ARBs	12	14	NS
Calcium channel blockers	7	9	NS
Metformin	10	9	NS
Pioglitazone	2	1	NS
Sulfonylurea	4	5	NS
Insulin	4	3	NS
Atorvastatin 5–20 mg/day	10	9	NS
Simvastatin 10–40 mg/day	13	9	NS
Rosuvastatin 5–20 mg/day	7	12	NS

ER-NA: extended release nicotinic acid, NS: not significant, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, HCTZ: hydrochlorothiazide, ACEIs: angiotensin converting enzyme inhibitors, ARBs: angiotensin receptor blockers. *Values are expressed as mean ± standard deviation (except for triglycerides which are expressed as median (range)).

the switch-to-rosuvastatin 40 mg compared with add-on-current-statin ER-NA/laropiprant group. In contrast, TGs and HDL-C levels were improved more with add-on-statin

ER-NA/laropiprant compared with switch-to-rosuvastatin 40 mg (Table 2). The observed BP reductions were not significantly correlated with HDL-C increase or other lipid changes in the add-on-statin ER-NA group (data not shown).

4. Discussion

This is the first study to directly compare the antihypertensive potential of switching to high-dose statin with add-on-current-statin ER-NA/laropiprant. We demonstrated that add-on-current-statin ER-NA/laropiprant but not the switch to rosuvastatin 40 mg is associated with significant reductions of both systolic and diastolic BP in patients with primary dyslipidemia, especially in the subgroup of hypertensives.

A growing body of evidence suggests that statins may reduce BP [5, 8, 9, 17, 18]. The effects of rosuvastatin on systemic and regional hemodynamics were evaluated in 2 hypertensive rat models (one genetically determined and one hypertensive-induced via inhibition of nitric oxide (NO) synthesis) [7]. Rosuvastatin reduced arterial BP in hypertensive rats and decreased total peripheral resistance [7]. Regional hemodynamics improved with rosuvastatin in both hypertensive models, as evidenced by increased blood flow and decreased vascular resistance [7]. These effects were independent of changes in plasma lipids. In addition, rosuvastatin has been associated with improved BP variability in genetically dyslipidemic mice (apolipoprotein E $-/-$) and reduced systolic BP in obese rats with chronic kidney injury [6, 19]. Moreover, in obese and dyslipidemic (leptin- and LDL-receptor-deficient) mice rosuvastatin reduced systolic BP to the same levels compared with age-matched wild type control mice despite incomplete correction of insulin resistance and regardless of dose [10].

The mechanisms by which statin may reduce BP remain unknown [20]. It is possible that statin effects on BP are mediated by endothelial function improvement. Of note, among the pleiotropic actions of rosuvastatin are the reduction of proinflammatory cytokines and endogenous NO synthase inhibitor levels, the promotion of NO function and peroxisome proliferator-activated receptor gamma (PPAR γ) expression, and the increase of superoxide dismutase 1 which represent major antioxidants in the vasculature [6, 7, 10]. Moreover, in a placebo-controlled study, rosuvastatin (10 mg/day) decreased P-selectin in 60 patients with pulmonary arterial hypertension (PAH) [21]. P-selectin is a crucial player in inflammation and thrombosis, and its reduction by rosuvastatin is relevant to the pathophysiological scenario of PAH and potentially to arterial BP [21]. Another possible mechanism is via increased 1,25 dihydroxyvitamin D levels [22]. Indeed, a growing body of evidence suggests that vitamin D may decrease BP [22, 23].

In our study, the switch to rosuvastatin 40 mg/day was not associated with significant BP reductions. A possible explanation could be that all patients were already receiving baseline statin treatment. As the BP-lowering effect of rosuvastatin has been demonstrated to be independent of

TABLE 2: Clinical and laboratory parameters at baseline and 3 months after treatment*.

	Baseline	3 months	Percentage change (%)
<i>Body weight (kg)</i>			
Switch-to-rosuvastatin 40 mg	79 ± 10	79 ± 9	0
Add-on-statin ER-NA/laropiprant	81 ± 10	81 ± 10	0
<i>SBP (mmHg)</i>			
Switch-to-rosuvastatin 40 mg	127 ± 14	127 ± 12	0
Add-on-statin ER-NA/laropiprant	134 ± 12	125 ± 10	-7††,§
<i>DBP (mmHg)</i>			
Switch-to-rosuvastatin 40 mg	80 ± 7	79 ± 6	-0.1
Add-on-statin ER-NA/laropiprant	81 ± 9	77 ± 6	-5†,§
<i>TC, mg/dL (mmol/L)</i>			
Switch-to-rosuvastatin 40 mg	226 ± 36 (5.8 ± 0.9)	180 ± 30 (4.7 ± 0.8)	-20††
Add-on-statin ER-NA/laropiprant	202 ± 42 (5.2 ± 1.1)	171 ± 37 (4.4 ± 1)	-15††
<i>Triglycerides, mg/dL (mmol/L)</i>			
Switch-to-rosuvastatin 40 mg	169 (150–189) [1.9 (1.7–2.1)]	156 (129–183) [1.8 (1.5–2.1)]	-7††
Add-on-statin ER-NA/laropiprant	164 (141–187) [1.9 (1.6–2.1)]	123 (97–148) [1.4 (1.1–1.7)]	-25††,§
<i>HDL-C, mg/dL (mmol/L)</i>			
Switch-to-rosuvastatin 40 mg	55 ± 9 (1.4 ± 0.2)	54 ± 9 (1.4 ± 0.2)	-0.2
Add-on-statin ER-NA/laropiprant	47 ± 11 (1.2 ± 0.3)	53 ± 16 (1.4 ± 0.4)	+13†,§
<i>LDL-C, mg/dL (mmol/L)</i>			
Switch-to-rosuvastatin 40 mg	142 ± 45 (3.7 ± 1.2)	98 ± 30 (2.5 ± 0.8)	-30††,‡
Add-on-statin ER-NA/laropiprant	112 ± 35 (2.9 ± 0.9)	91 ± 34 (2.4 ± 0.9)	-19††
<i>Non-HDL-C, mg/dL (mmol/L)</i>			
Switch-to-rosuvastatin 40 mg	175 ± 33 (4.5 ± 0.9)	127 ± 26 (3.3 ± 0.7)	-40††
Add-on-statin ER-NA/laropiprant	155 ± 37 (4.0 ± 1)	118 ± 34 (3.1 ± 0.9)	-24††

SBP: systolic blood pressure, DBP: diastolic blood pressure, ER-NA: extended release nicotinic acid, TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, non-HDL-C: non-high-density lipoprotein cholesterol.

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

† $P < .01$ versus baseline.

†† $P < .001$ versus baseline.

‡ $P < .01$ versus and switch-to-rosuvastatin 40 mg group.

§ $P < .01$ versus the add-on-statin ER-NA/laropiprant group.

dose and changes in lipids, at least in animal models, it is possible that the switch to high-dose rosuvastatin does not result in any further reduction in BP compared with preexisting statin treatment [6, 7, 9, 10].

Despite the use of NA for approximately 50 years, there are only few reports on the effects of NA on BP [11, 24, 25]. In one study NA was intravenously infused to 11 normotensive and 10 hypertensive subjects [26]. In the normotensives, systolic, diastolic, and mean BP and pulse pressure were not affected by NA. In contrast, the hypertensive subjects experienced a decrease in mean BP from 105 ± 2 mmHg to 100 ± 3 mmHg ($P < .01$) accompanied by significant decreases in systolic, diastolic, and pulse pressures. [26] Another study

reached similar results, supporting that NA (500 mg/day for 7 days and then 1 g/day for further 7 days) does not have an acute effect on BP in normotensive subjects [27]. A post-hoc analysis of the Coronary Drug Project (CDP) demonstrated that 1-year therapy with NA in patients with metabolic syndrome was associated with a 2.2 mmHg reduction of systolic BP compared with a rise of 0.8 mmHg in the placebo group ($P < .0001$) [28]. Additionally, diastolic BP declined by 2.9 mmHg compared with 0.9 mmHg decrease in the placebo group ($P < .0001$) [28]. In a post-hoc analysis of a 24-weeks, phase 3 trial, 1613 dyslipidemic patients were randomized in ER-NA alone or ER-NA/laropiprant combination or placebo [15]. BP decreased with ER-NA, while laropiprant

did not attenuate or abolish this effect [15]. Specifically, the placebo-adjusted mean changes from baseline in systolic BP were -2.2 and -3.1 mmHg in the ER-NA and ER-NA/laropiprant groups ($P < .05$ and $P < .001$, resp.), while similar changes were reported for diastolic BP (-2.7 and -2.5 mmHg in the ER-NA and ER-NA/laropiprant groups, respectively, both $P < .001$) [15]. Of note, the reduction of systolic BP in the ER-NA and ER-NA/laropiprant groups was more pronounced in patients not receiving antihypertensive treatment compared with those on such treatment. On the contrary, diastolic BP decreased similarly in all patients receiving ER-NA or ER-NA/laropiprant regardless of concomitant antihypertensive therapy [15]. There were also a few cases reported of hypotension (in 0.3%, 0.0%, and 0.7% of patients receiving ER-NA, ER-NA/laropiprant and placebo, resp.) and orthostatic hypotension (in 0.1%, 0.2% and 0.0% of patients receiving ER-NA, ER-NA/laropiprant and placebo, resp.) [15]. In contrast, in a smaller ($n = 412$) and shorter study (8 weeks), the combination of ER-NA (1–2 g/day) with laropiprant did not significantly alter BP levels [29].

The mechanisms by which NA can reduce BP remain unknown. Studies with NA and laropiprant suggest that the latter does not affect BP [15, 30]. Thus, it is unlikely that these changes are mediated by prostaglandin D₂ or cutaneous vasodilatation. Another possible mechanism may be the improvement in endothelial function, as HDL promotes NO endothelial generation [31]. Thus, the NA-induced elevation of HDL may result in a NO-mediated decrease of BP [31].

In our study, add-on-statin ER-NA/laropiprant was associated with significant BP reductions, mainly in hypertensive subjects. The observed BP reductions were not significantly correlated with HDL-C increase or other lipid changes. Thus, the ER-NA/laropiprant-induced BP lowering may be independent of lipid changes and may be associated with the pleiotropic effects of this agent [24]. NA apart from raising HDL improves several pleiotropic properties of HDL including improved capacity of HDL to stimulate endothelial NO, to reduce superoxide production, and to promote endothelial progenitor cell-mediated endothelial repair which may be beneficial for endothelial function [32]. Moreover, NA has been directly associated with the reduction of asymmetric dimethylarginine (ADMA), a methylated amino acid that causes endothelial dysfunction by competitive inhibition of the NO synthase [33, 34]. Of note, although ER-NA/laropiprant-associated BP reduction was numerically similar between normotensives and hypertensives, it was significant only in hypertensive subjects. This is in agreement with a previous study [26]. However, the small number of patients in the normotensive subgroup does not allow firm conclusions.

Both treatments induced favourable changes in lipid profile. We noticed more pronounced reduction in LDL-C in the switch-to-rosuvastatin 40 mg group compared with the add-on-statin ER-NA/laropiprant group. As expected, TGs and HDL-C were improved more with the add-on-statin ER-NA/laropiprant compared with the switch-to-rosuvastatin 40 mg.

5. Study Limitations and Strengths

A major limitation of our study is its open-label design. On the other hand, it was an adequately powered randomized study that used a validated method for the assessment of BP. Moreover, all laboratory determinations were performed blindly with regard to treatment allocation. This study design is relevant to every day clinical practice when the treating physician is in dilemma over what to do in a patient who has failed to achieve lipid targets while on conventional statin treatment.

Patients with hypertension had adequately controlled BP readings before study commence. The BP-lowering effect of NA may be more pronounced in inadequately controlled hypertensives, but further research in this field is needed.

6. Conclusion

The addition of ER-NA/laropiprant to a conventional statin regimen, but not the switch to high-dose rosuvastatin, is associated with significant reductions of both systolic and diastolic BP in dyslipidemic patients, especially in those with hypertension. Addition of ER-NA/laropiprant to a conventional statin regimen may further improve both BP and lipid profile in hypertensives who have not achieved lipid targets.

Conflict of Interests

The authors state no conflict of interests and have received no payment in preparation of this manuscript. Some of the authors have given talks, attended conferences, and participated in trials and advisory boards sponsored by various pharmaceutical companies, including Merck Sharp and Dohme (MSD).

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