

# Evaluation in Patients with High NORMAL Blood Pressure of a Supplement Containing Arginine, Lactobacillus Plantarum Lp-LDL, Coenzyme Q10 and Vitamin B1: A PILOT Study

Giuseppe Derosa<sup>1,2,3,\*</sup>, Giovanni Gaudio<sup>4</sup>, Angela D'Angelo<sup>1,2</sup>, Pamela Maffioli<sup>1</sup>

<sup>1</sup>Department of Internal Medicine and Therapeutics, University of Pavia, PAVIA, Italy

<sup>2</sup>Laboratory of Molecular Medicine, University of Pavia, PAVIA, Italy

<sup>3</sup>Responsible Diabetes Area of Italian Nutraceutical Society (SINut)

<sup>4</sup>Internal Medicine Division, Ospedale Angelo Bellini, Somma Lombardo, VARESE, Italy

\*Corresponding author: [giuseppe.derosa@unipv.it](mailto:giuseppe.derosa@unipv.it)

Received June 06, 2020; Revised July 07, 2020; Accepted July 15, 2020

**Abstract Aim:** to evaluate the effects of a nutraceutical containing Arginine, Lactobacillus Plantarum Lp-LDL, Coenzyme Q10 and Vitamin B1 in patients with high normal blood pressure on the levels of systolic (SBP) and diastolic blood pressure (DBP). **Methods:** we enrolled 40 patients of both sexes, with high normal pressure (SBP values between 130-139 mmHg and/or DBP between 85-89 mmHg) according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension. Patients were consecutively enrolled to take nutraceutical for 3 months and it is self-administered once a day during the breakfast. **Results:** no significant variations of BMI or circumferences were recorded with nutraceutical from baseline. A slight reduction of FPG was recorded, although this variation was not significant. Significant reductions were obtained in SBP ( $p < 0.05$ ) and DBP ( $p < 0.05$ ). No significant HR variation was observed from baseline. A significant TC and LDL-C decrease were observed after 3 months ( $p < 0.05$ , respectively). No significant HDL-C, and Tg variations were obtained after 3 months. No significant reduction of Hs-CRP was recorded compared to baseline. No significant variations of transaminases were recorded during the study, and creatinine value was not significantly modified compared to baseline. **Conclusions:** a nutraceutical containing Arginine, Lactobacillus Plantarum Lp-LDL, Coenzyme Q10 and Vitamin B1 could be helpful in improving high normal blood pressure, and hypercholesterolemia, two of the major risk factors for vascular events.

**Keywords:** arginine, Lactobacillus Plantarum Lp-LDL, Coenzyme Q10, Vitamin B1, blood pressure

**Cite This Article:** Giuseppe Derosa, Giovanni Gaudio, Angela D'Angelo, and Pamela Maffioli, "Evaluation in Patients with High NORMAL Blood Pressure of a Supplement Containing Arginine, Lactobacillus Plantarum Lp-LDL, Coenzyme Q10 and Vitamin B1: A PILOT Study." *Journal of Food and Nutrition Research*, vol. 8, no. 6 (2020): 273-278. doi: 10.12691/jfnr-8-6-5.

## 1. Introduction

International guidelines for the management of hypertension [1] and cardiovascular disease risk [2] suggest that lifestyle correction is the first step in the treatment of patients with high normal hypertension (pre-hypertension). There is no doubt that a correct dietary approach, especially if accompanied by an increase in physical activity, is associated with a significant reduction in cardiovascular risk in the general population and in the hypertensive patient. However, often a change in lifestyle is not easy to achieve and, even if you manage to achieve it, the results are seen in the long term, which often discourages the patient from continuing [3]. A possible support for lifestyle correction could be the use of some supplements that have shown an anti-hypertensive

action, and which, if effective, could lead to a significant reduction in blood pressure, also in addition to anti-hypertensive standard therapy [4]. In fact, meta-analyses of randomized, placebo-controlled studies have been published in the literature, in which various substances have been shown to induce pressure drops equal to 2-8 mmHg of systolic pressure and 2.5 mmHg of diastolic pressure [5,6]. Some of these substances require very high dosages, like omega-3, others are too expensive, like lactotripeptides, while others are burdened by side effects, such as garlic extracts [7]. Furthermore, other supplements, such as nitric oxide precursors, magnesium and folic acid, can improve endothelial function and consequently reduce pressure values [8,9].

Among various nutraceuticals, a combination of L-arginine with B vitamins proved to be more effective than placebo in improving and restoring impaired endothelial function and lowering blood pressure in

patients with mild to moderate blood pressure elevation [10]. Also coenzyme Q10 proved to have a positive impact on blood pressure in humans [11]. Moreover, recombinant *Lactobacillus plantarum* showed to be effective and safe in the treatment of hypertension: oral administration of recombinant *Lactobacillus plantarum* dramatically decreases blood pressure, endothelin and Angiotensin II production, and triglyceride levels with no observed side effects, indicating its potential application in hypertension and related diseases [12].

In this context, the aim of this pilot study was to explore if the experimental design is correct in order to reject or not the hypothesis that the nutraceutical proposed could be useful in reducing blood pressure values. In particular the hypothesis is to evaluate the effects of a supplement containing Arginine, *Lactobacillus Plantarum* Lp-LDL, Coenzyme Q10 and Vitamin B1 [Tensred plus® (nutraceutical)] (Table 1) in patients with pre-hypertension on the levels of systolic (SBP) and diastolic blood pressure (DBP).

## 2. Materials and Methods

### 2.1. Study Design

The study was conducted according to the ethical rules of the 1994 Helsinki Declaration and all patients formally consented to the study after a full study explanation [13].

#### 2.1.1. Patients

We enrolled 40 patients aged  $\geq 18$  years of both sexes, with pre-hypertension (SBP values between 130-139 mmHg and/or DBP between 85-89 mmHg) according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension [1] and without organ damage and history of cardiovascular diseases. Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone.

Patients were excluded if they had type 1 or type 2 diabetes mellitus, impaired hepatic function (defined as transaminases and/or gamma-glutamyl transpeptidase level higher than the three times the upper limit of normal [ULN] for age and sex), impaired renal function (defined as serum creatinine level higher than the ULN for age and sex), or gastrointestinal disorders; current or previous evidence of ischemic heart disease, heart failure, or stroke; malignancy, and significant neurological or psychiatric disturbances, including alcohol or drug abuse. Excluded medications (within the previous 3 months) included hypoglycemic agents, laxatives,  $\beta$ -agonists (other than inhalers), cyproheptadine, anti-depressants, anti-serotonergics, phenothiazines, barbiturates, oral corticosteroids, and anti-psychotics. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

### 2.2. Treatments

Patients were consecutively enrolled to take nutraceutical for 3 months and it is self-administered once a day during the breakfast. Nutraceutical was supplied as tablets in coded bottles. Medication compliance was assessed by

counting the number of pills returned at the time of specified clinic visits. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. Nutraceutical was provided free of charge.

### 2.3. Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs (blood pressure and heart rate), a 12-lead electrocardiogram, measurements of, a 12-lead electrocardiogram, measurements of height and body weight, calculation of body mass index (BMI), assessment of fasting plasma glucose (FPG), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (Tg), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and high-sensitivity C-reactive protein (Hs-CRP).

All parameters were assessed at baseline and after 3 months since the study start. All plasmatic variables were determined after a 12-hour overnight fast, with the exception of PPG. Venous blood samples were drawn by a research nurse for all patients between 8:00 AM and 9:00 AM. We used plasma obtained by addition of Na<sub>2</sub>-EDTA, 1 mg/mL, and centrifuged at 3000g for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for  $\leq 3$  months. Laboratory technicians drew blood samples and the biologist responsible for the laboratory performed the assays. All measurements were performed in a central laboratory.

Body mass index was calculated by the investigators as weight in kilograms divided by the square of height in meters.

Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay coefficients of variation (CsV)  $< 2\%$  [14].

Total cholesterol and Tg levels were determined using fully enzymatic techniques [15,16] on a clinical chemistry analyzer (Hitachi 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1.0% and 2.1% for TC measurement, and 0.9% and 2.4% for Tg measurement, respectively. HDL-C level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid [17]; intra- and interassay CsV were 1.0% and 1.9%, respectively. LDL-C level was calculated using the Friedewald formula [18].

Transaminases and creatinine were evaluated in central laboratory according to standard methods.

High sensitivity C-reactive protein was measured with use of latex-enhanced immunonephelometric assays on a BN II analyser (Dade Behring, Newark, Delaware, USA). The intra- and interassay CsV were 5.7% and 1.3%, respectively [19].

### 2.4. Safety Measurements

Treatment tolerability was assessed using an accurate interview of patients by the clinicians at each study visit, and comparisons of clinical and laboratory values with

baseline levels. Safety monitoring included physical examination, vital sign assessment, weight, electrocardiogram, adverse events, and laboratory tests. Liver and kidney function was evaluated by measurement of transaminases (AST, ALT), and creatinine, respectively. All adverse events were recorded.

## 2.5. Statistical Analysis

An intention-to-treat (ITT) analysis was conducted in patients who had received  $\geq 1$  dose of study medication and had a subsequent efficacy observation. Patients were included in the tolerability analysis if they had received  $\geq 1$  dose of trial medication. Continuous variables were tested using a two-way repeated measures analysis of variance (ANOVA). Intervention effects were adjusted for additional potential confounders using analysis of covariance. A 1-sample *t* test was used to compare values obtained before and after treatment administration. Statistical analysis of data was performed using the Statistical Package for Social Sciences software version 14.0 (SPSS Inc., Chicago, Illinois, USA). Data are presented as mean (SD). For all statistical analyses,  $p < 0.05$  was considered statistically significant [20].

## 3. Results

### 3.1. Study Sample

A total of 40 patients were enrolled in the trial. All patients completed the study.

### 3.1.1. Anthropometric Parameters and Glycemic Value

No significant variations of BMI or circumferences were recorded with nutraceutical from baseline. BMI change was  $-0.1 \text{ Kg/m}^2$ , while Abd. Circ., Waist Cir., and Hip Circ, were  $-0.1 \text{ cm}$ ,  $-0.2 \text{ cm}$ , and  $-0.2 \text{ cm}$ , respectively.

A slight reduction of FPG was recorded, although this variation was not significant ( $-2.2 \text{ mg/dl}$ ) (Table 2).

### 3.1.2. Blood Pressure and heart Rate

Significant reductions were obtained in SBP ( $-4.1 \text{ mmHg}$ ,  $p = 0.041$ ) and DBP ( $-3.0 \text{ mmHg}$ ,  $p = 0.044$ ). No significant HR variation ( $-1.1 \text{ b/min}$ ) was observed from baseline (Table 2).

### 3.2. Lipid Profile

A significant TC and LDL-C decrease were observed after 3 months ( $p = 0.040$ , and  $p = 0.042$ , respectively). Total cholesterol change from baseline was  $-13.5 \text{ mg/dl}$ , and LDL-C change was  $-11.4 \text{ mg/dl}$ , respectively. No significant HDL-C, and Tg variations were obtained after 3 months. In particular, if an increase in HDL-C was not observed ( $-0.9 \text{ mg/dl}$ ), a decrease trend in Tg ( $-6 \text{ mg/dl}$ ) was instead observed (Table 2).

Table 1. Composition of Tensred plus®

Ingredients	Daily intake
L-Arginine	200 mg
Coenzyme Q10	50 mg
Lactobacillus Plantarum Lp-LDL	4 x 10 <sup>9</sup> CFU
Vitamin B1 (Thiamine)	1.1 mg

CFU: colony-forming unit.

Table 2. Nutraceutical treatment at baseline and after 3 months

	Baseline	3 months	$\Delta$	%	<i>p</i> value
N	40	40	-	-	-
sex (M/F)	24/16	24/16	-	60/40	-
Age (years)	54.2 $\pm$ 4.7	-	-	-	-
Smoking status (M/F)	9/6	9/6	-	22.5/15.0	-
Height (m)	1.67 $\pm$ 0.06	-	-	-	-
Weight (Kg)	78.9 $\pm$ 7.8	78.7 $\pm$ 7.5	-0.2	-0.3	0.864
BMI (Kg/m <sup>2</sup> )	28.3 $\pm$ 2.9	28.2 $\pm$ 2.7	-0.1	-0.4	0.932
Abd. Cir. (cm)	95.7 $\pm$ 3.8	95.6 $\pm$ 3.0	-0.1	-1.0	0.926
Waist Cir. (cm)	89.9 $\pm$ 3.1	89.7 $\pm$ 2.9	-0.2	-0.2	0.857
Hip Cir. (cm)	101.3 $\pm$ 4.7	101.1 $\pm$ 3.7	-0.2	-0.2	0.836
SBP (mmHg)	135.8 $\pm$ 3.9	131.7 $\pm$ 3.2*	-4.1	-3.0	0.041
DBP (mmHg)	87.1 $\pm$ 1.7	84.1 $\pm$ 1.5*	-3.0	-3.4	0.044
HR (b/min)	76.2 $\pm$ 5.4	75.1 $\pm$ 5.2	-1.1	-1.4	0.457
FPG (mg/dl)	92.4 $\pm$ 11.8	90.2 $\pm$ 11.2	-2.2	-2.4	0.082
TC (mg/dl)	204.7 $\pm$ 15.3	191.2 $\pm$ 10.4*	-13.5	-6.6	0.040
LDL-C (mg/dl)	133.4 $\pm$ 12.1	122.0 $\pm$ 9.6*	-11.4	-8.5	0.042
HDL-C (mg/dl)	46.3 $\pm$ 8.1	45.4 $\pm$ 7.3	-0.9	-1.9	0.093
Tg (mg/dl)	124.9 $\pm$ 21.6	118.9 $\pm$ 19.5	-6.0	-4.8	0.058
AST (IU/l)	20.4 $\pm$ 7.8	21.6 $\pm$ 8.2	+1.2	+5.9	0.732
ALT (IU/l)	24.8 $\pm$ 9.1	25.7 $\pm$ 10.8	+0.9	+3.6	0.694
Creatinine (mg/dl)	0.91 $\pm$ 0.13	0.88 $\pm$ 0.11	-0.3	-33.0	0.091
Hs-CRP (mg/l)	1.1 $\pm$ 0.5	1.0 $\pm$ 0.4	-0.1	-9.1	0.084

Data are expressed as mean  $\pm$  standard deviations

\* $p < 0.05$  vs baseline

M: males; F: females; BMI: body mass index; Abd. Cir.: abdominal circumference; Waist Cir.: waist circumference; Hip Cir.: hip circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; Tg: triglycerides; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Hs-CRP: high-sensitivity C-reactive protein.

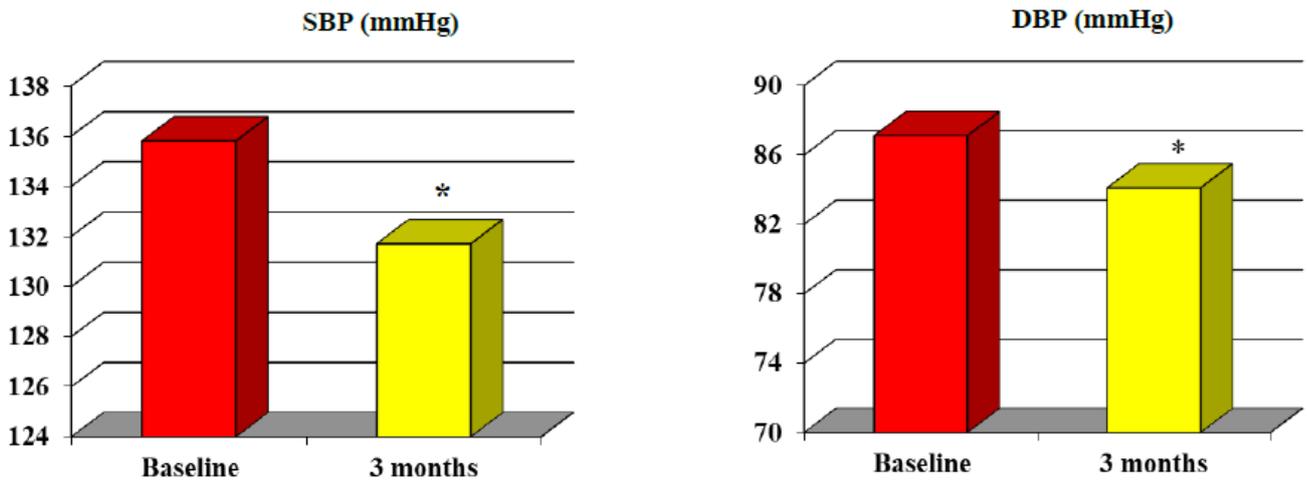


Figure 1. Systolic and diastolic blood pressure variation during the study with the nutraceutical (\* $p < 0.05$  vs baseline)

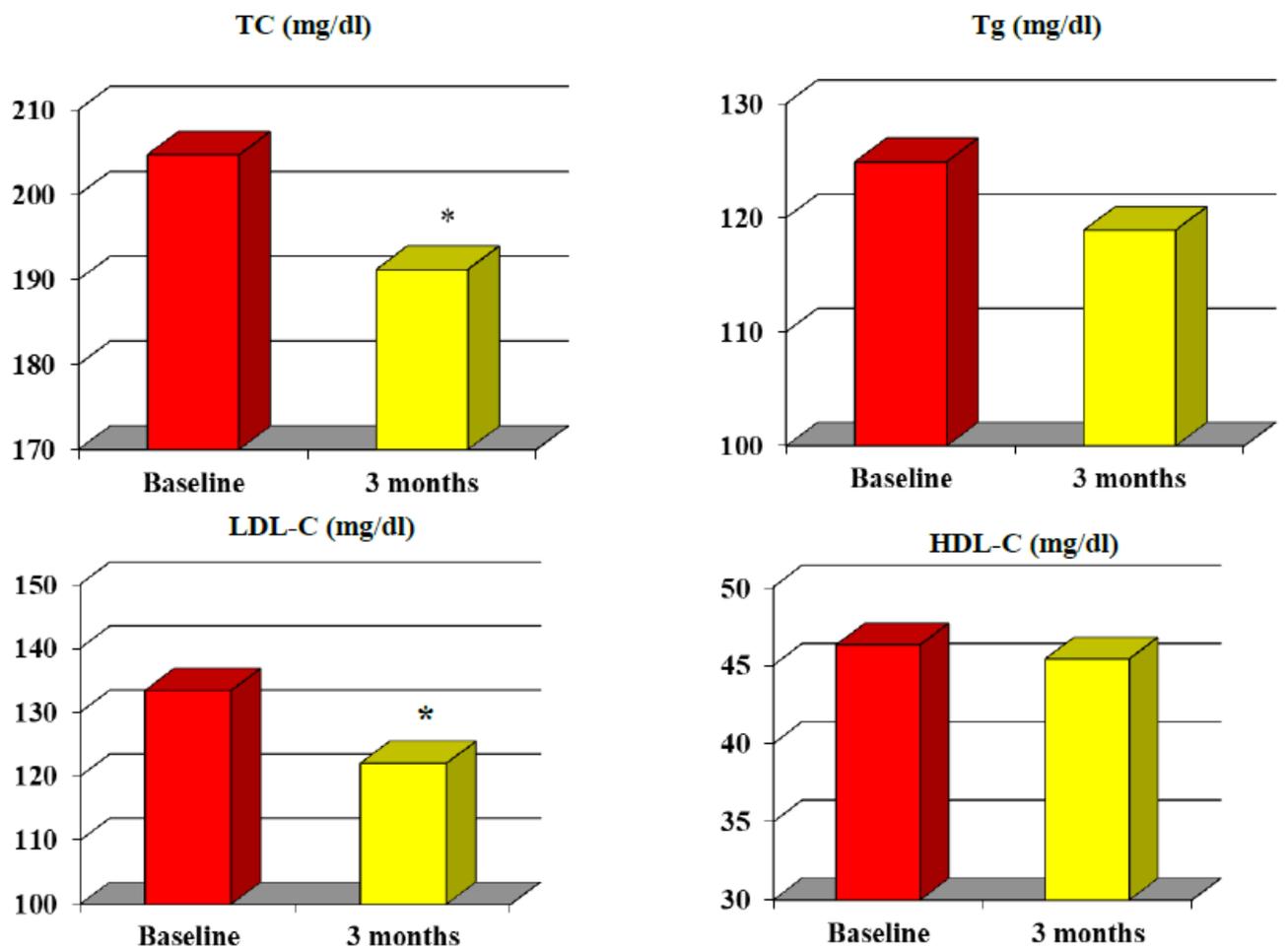


Figure 2. Lipid profile variation during the study with the nutraceutical (\* $p < 0.05$  vs baseline)

### 3.3. Inflammatory Parameter

No significant reduction of Hs-CRP was recorded compared to baseline (-0.1 mg/l) (Table 2).

### 3.4. Safety Parameters

No significant variations of transaminases were recorded during the study. Alanine aminotransferase change from baseline was +1.2 IU/l, while ALT change was +0.9 IU/l, respectively. Creatinine value was not

significantly modified compared to baseline (-0.3 mg/dl) (Table 2).

## 4. Discussion

Arginine, Lactobacillus Plantarum Lp-LDL, Coenzyme Q10 and Vitamin B1 decreased SBP and DBP in patients with pre-hypertension; from the results, we also noticed an improvement in TC and LDL-C: this is what we saw in the pilot study, which we conducted for 3 months.

While nutraceuticals for dyslipidemia have culturally entered the facilities available to the doctors, especially in primary prevention, this has not yet been defined for hypertension. In particular, the latest European ESC/ESH Guidelines have highlighted how important it is to recognize patients with pre-hypertension and drug treatment could only be considered when the cardiovascular risk is very high for an ascertained cardiovascular disease, especially coronary heart disease [1].

This type of approach will involve on the one hand the identification of a much higher number of hypertensive patients and on the other hand a high number of patients with non-optimized blood pressure. Since the same Guidelines emphasize how this phenomenon does not necessarily have to be managed with a reinforcement of the share of drugs, then this can become very interesting to find alternatives that can make patients more adherent to lifestyle changes and make these changes more effective in reducing blood pressure levels without causing adverse events [6]. Currently in the literature, there are few, but certainly more numerous reviews on the topic "Nutraceuticals and blood pressure" compared to studies with nutraceuticals in patients with pre-hypertension or hypertension. Furthermore, this is one of the few, if not the only pilot study that has currently evaluated only patients with pre-hypertension. Some studies that can be mentioned have considered patients having both pre-hypertension and grade 1 hypertension.

Our pilot study demonstrated a small, but significant, reduction in SBP (-3.0 %) and DBP (-3.4 %) values in patients with pre-hypertension.

In general, a reduction of a few mmHg may not be worthy of attention, but if we look at the literature, we must say that, although we are talking in this case of hypertensive patients, the HOPE study [21] had shown that a reduction of only 3.5 mmHg of SBP and 1.5 mmHg of DBP led to a reduction in the incidence of myocardial infarction from 12.3 to 9.9% and total mortality from 12.2 to 10.4%. Furthermore, in the MICRO-HOPE study [22] the reduction in SBP (2.4 mmHg) and DBP (1.0 mmHg) led to a reduction in cardiovascular events of 25-30%. Several authors [23] however also think that, having used the two trials an ACE inhibitor (ramipril), not only the reduction of blood pressure is responsible for these cardiovascular benefits, but could also be attributable to a specific action of the ACE -inhibitors at the level of the heart and vessels [24].

Cicero AFG et al. [6] showed a small, but also significant reduction in blood pressure, in a study that evaluated patients with pre-hypertension or patients with grade 1 hypertension treated with placebo compared nutraceutical containing Beetroot dry extract, magnesium, Vitamin C, Vitamin B1 and Vitamin D. However, the study does not show how many patients were with pre-hypertension, their blood pressure average at the beginning or at the end of the treatment, since the two groups are united by a single average. Anyway, he demonstrated a significant reduction of 8 mmHg (morning SBP) and a significant reduction of 7 mmHg (morning DBP) in the group treated with nutraceutical, even if he observed also a significant reduction of 6 mmHg (morning SBP) in the placebo group.

A similar study, that is enrolling the same group of patients thus formed, was conducted by Shen T et al. [25]. One group was treated with a product containing Omega-3 fish oil, L-carnitine fumarate, Coenzyme Q10, folic acid, Vitamin E, Vitamin B6, Vitamin B12, and lipoic acid compared to the other group treated with soybean oil. He observed a significant decrease of 2.3 mmHg in DBP in the first group, while a nonsignificant reduction was obtained in SBP.

Another study by Mazza A et al. [26] evaluated the variation of the lipid profile with a nutraceutical based on red yeast rice, Berberine, Coenzyme Q10, folic acid, and chrome in patients with pre-hypertension compared to another group treated with diet only. He declares a nonsignificant achievement of blood pressure decrease, both systolic and diastolic, by not showing the values.

In this study, a significant reduction was observed in TC (31 mg/dl; -13.2 %), LDL-C (27 mg/dl; -17.4 %), Tg (33 mg/dl; -23.7 %) and a significant increase in HDL-C (3.4 mg/dl; + 6.6 %).

Also in our pilot study we also noticed a significant reduction in TC (13.5 mg/dl; -6.6 %) and LDL-C (11.4 mg/dl; -8.5 %), while the decreases in HDL-C (0.9 mg/dl; -1.9 %) and Tg (6 mg/dl; -4.8 %) were not significant, although the latter seems to have a downward trend.

In the study of Shen T. et al. [25] the Tg values have not been evaluated. Total cholesterol (-7.7 mg/dl; -3.6%), LDL-C (-15.5 mg/dl; -10.8%) and HDL-C (+23.2 mg/dl; +48.3%) were significantly improved, in particular in the group in which a significant reduction in DBP was achieved.

Finally, in the same study by Cicero AFG et al. [6] only the TC value was taken into consideration, which was significantly decreased (22 mg/dl; -11.7 %) in the group receiving nutraceutical.

This study has some limitations that need to be mentioned. First of all, it is a pilot study, which wanted to explore if the experimental design is correct in order to reject or not the hypothesis that the nutraceutical proposed could be useful in reducing blood pressure values. Without any doubt, future studies must be planned including a placebo comparison group or other groups with the active principles by separate to evaluate if there is a synergic action when the compounds are taken together in a single pill. Moreover, a double blind study design will be needed. Another point is the sample size, which supposedly needs to be expanded.

## 5. Conclusion

In conclusion, this pilot study showed that a nutraceutical containing Arginine, Lactobacillus Plantarum Lp-LDL, Coenzyme Q10 and Vitamin B1 could be helpful in improving high normal blood pressure, and hypercholesterolemia, two of the major risk factors for vascular events.

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