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# Efficacy and tolerability of combined treatment with L-carnitine and simvastatin in lowering lipoprotein(a) serum levels in patients with type 2 diabetes mellitus

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**Abstract**

Lipoprotein(a) [Lp(a)] concentration is generally related to coronary artery disease (CAD) and cerebrovascular disease. However, at present, few interventions are available to lower Lp(a) concentrations. We investigated the effects of L-carnitine, co-administered with simvastatin, on hyper-Lp(a) in patients with type 2 diabetes mellitus. We conducted an open, randomised, parallel-group study, in one investigational center (University hospital). Fifty-two patients with type 2 diabetes mellitus, a triglyceride serum levels <400 mg/dL (<4.5 mmol/L), and Lp(a) serum levels >20 mg/dL (0.71 mmol/L) were randomised to receive simvastatin alone ($n = 26$) or simvastatin plus L-carnitine ($n = 26$) for 60 days. Simvastatin was administered, in both groups, at a dosage of 20 mg/day, while L-carnitine was administered at a dosage of 2 g/day once daily. Both treatments were given orally. Serum levels of triglycerides, total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol (total cholesterol minus HDL cholesterol), apolipoprotein B, and Lp(a) were measured at baseline and 60 days after starting treatment. No difference in time by groups (simvastatin and simvastatin plus L-carnitine) were observed in the reduction of LDL cholesterol, non-HDL cholesterol, and apoB serum levels. On the other hand, Lp(a) serum levels increase from baseline to 60 days in the simvastatin group alone versus a significant decrease in the combination group. Our findings provide support for a possible role of combined treatment with L-carnitine and simvastatin in lowering Lp(a) serum levels in patients with type 2 diabetes mellitus than with simvastatin alone. Our results strongly suggest that L-carnitine may have a role among lipid-lowering strategies.


*Keywords:* Lipoprotein(a); Coronary artery disease; L-Carnitine; Simvastatin; Type 2 diabetes mellitus

## 1. Introduction

Lipoprotein(a) [Lp(a)], a unique lipoprotein particle in which the protein component consists of apolipoprotein B bound by a disulfide bond to apolipoprotein (a) (apo(a)), has atherogenic and thrombotic properties [1], and its concentration in human plasma is genetically determined, with at least 90% of the variation determined by variation within the gene for apo(a) [2]. Increased plasma concentration of Lp(a) has been associated with increased risk of coronary artery disease (CAD) in numerous retrospective case-control and prospective studies, with few notable exceptions [3]. This association is not confirmed among the elderly [4–6], despite a higher Lp(a) serum level found in centenarians compared to normolipidemic younger controls [7,8]. The results of the Italian Longitudinal Study on Aging (ILSA) suggested that elevated serum concentration of Lp(a) may be a risk factor of CAD in

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the elderly only in the presence of type 2 diabetes mellitus and high serum low-density lipoprotein (LDL) cholesterol levels [9]. Finally, increased plasma concentration of Lp(a) has been associated with cerebrovascular disease (CVD) [10] and we found an association between higher Lp(a) serum levels and Alzheimer's disease (AD) independently of apolipoprotein E genotype [11].

The major drug classes, including 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA)-reductase inhibitors (statins), fibrates, and resins, do not appear to result in any clear reduction of Lp(a) levels [12–15]. In particular, in patients placed on statins contrasting findings have been reported [16–25], but the beneficial effect of lowered total cholesterol and LDL cholesterol levels may be partly blunted by a concomitant increase in Lp(a) levels [17–19]. At present, only high doses nicotinic acid (4 g/day) [26,27], and two nicotinic acid derivatives with fewer side effects such as acipimox [28,29] and niceritrol [30], or estrogen replacement therapy [31] have clearly resulted in Lp(a) reductions.

Promising results have also been obtained in patients with primary hyperlipoproteinemia [32] and in our previous study on subjects with a wide range of Lp(a) levels [33], suggesting a positive impact of L-carnitine treatment in inducing a less atherogenic plasma lipoprotein fatty acid profile. In fact, in patients with type 2 diabetes, combined therapy with simvastatin (20 mg/day) and L-carnitine (2 g/day) demonstrated greater lipid-lowering efficacy than simvastatin alone, especially with regard to triglyceride levels [34]. Furthermore, in a recent double-blind placebo controlled study, L-carnitine (2 g/day) significantly reduced Lp(a) levels in subjects with hyper-Lp(a) (serum Lp(a) levels ranging between 40 and 80 mg/dL) [35]. Finally, in 94 subjects newly diagnosed with type 2 diabetes mellitus who were managed through dietary restriction alone, after 3 and 6 months, L-carnitine (2 g/day) significantly lowered the plasma Lp(a) level compared with placebo [36]. On the basis of these previous reports, in the present study we assessed the effects of combined treatment with L-carnitine and simvastatin compared with simvastatin alone on serum lipids, lipoproteins, and apolipoproteins in patients with type 2 diabetes mellitus. The tolerability of such treatments was also investigated.

## 2. Methods

### 2.1. Patients

Between December 2002 and July 2004, outpatients attending the Center for Lipoprotein Metabolism Disease, Department of Geriatrics, Bari University Hospital, Italy, were recruited for the study and underwent a laboratory assessment at both baseline and 60 days of follow-up. After discontinuing all lipid-lowering drugs and supplements and/or treatment with other drugs known to affect mitochondrial metabolism (i.e., glibenclamide and benzodiazepines), patients entered a 6-week dietary lead-in period, during which their ability to comply with a diet that restricts total fat to less than 30% of total energy, saturated fat to less than 7% of energy, and cholesterol to less than 200 mg/day was assessed. Eligible patients had type 2 diabetes mellitus, a triglyceride serum levels <400 mg/dL (<4.5 mmol/L), and Lp(a) serum levels >20 mg/dL (>0.71 mmol/L) at two consecutive measurements at 4 and 5 weeks from the dietary lead-in period. In fact, at concentrations exceeding 20 mg/dL the relative risk for the development of CAD is markedly increased, particularly when Lp(a) levels >30 mg/dL [3]. All subjects received a comprehensive physical examination, with an ECG and a battery of biochemical/hematological tests for the measurement of lipids and other components that were part of the safety assessment. No patient was suffering, or had suffered, from renal or neoplastic diseases, as well not presented seizure history. After complete description of the study, written informed consent was obtained from all patients. The trial has been previously approved by the Ethics Committee of the University of Bari. The trial was conducted according to the Guidelines for Good Clinical Practice and the Declaration of Helsinki.

### 2.2. Interventions, study design, and evaluation parameters

Patients were randomly assigned to receive either 20 mg of simvastatin (one tablet at bed-time) or 20 mg of simvastatin plus 2 g L-carnitine orally daily (two 1 g bottles in the morning). The duration of treatment was 60 days. The study was in open regardless the therapy but the patients and all study personnel were unaware of the results of laboratory measurements. At each visit, they underwent a complete physical examination and blood samples were taken to measure total cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol (total cholesterol minus HDL cholesterol), LDL cholesterol, triglycerides, apolipoprotein B (apoB), and Lp(a). In particular patients were monitored for event of abnormal liver-function results, elevations in creatine phosphokinase levels, or myalgias or transient nausea/vomiting, abnormal cramps, and diarrhea.

### 2.3. Clinical examination and laboratory determinations

The following medical conditions were identified as present or absent in all participants by means of a screening questionnaire: type 2 diabetes mellitus, coronary artery disease (myocardial infarction and angina pectoris), hypertension, and stroke. The suspect diagnoses were confirmed with a standardized clinical examination by a certified geriatrician, neurologist, or internist. Details on the diagnostic criteria used to define the investigated conditions have been presented elsewhere [37]. In particular, subjects with type 2 diabetes mellitus were identified with a two-phases procedure. In Phase 1, each subject was administered a screening questionnaire, a series of brief screening tests to identify suspect cases for further investigation, and a clinical evaluation;

in Phase 2, suspected cases were clinically confirmed with a standardized clinical examination by a certified internist [37]. The criteria for diagnosis of type 2 diabetes mellitus were adopted from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [38,39]. Demographic variables and concurrent medications were selected from a comprehensive set of measures gathered at baseline.

Blood samples were obtained early in the morning after a 13-h overnight fast. Serum was removed after centrifugation at $1500 \times g$ for 20 min and it was rapidly frozen and stored at $-80\,^{\circ}C$ until Lp(a) evaluation, except for the volume needed for lipid determination analyzed in the same day. Samples were stored using small-volume storage vials that were thawed only once at the time of assay to avoid the differential loss of Lp(a) antigenicity seen at higher storage temperature [40]. Serum Lp(a) concentrations were measured in duplicate using a commercial enzyme-linked immunosorbent assay (Immuno GMBH, Heidelberg, Germany). Serum total cholesterol, triglycerides, and HDL cholesterol were measured by standard enzymatic-colorimetric methods (Boehringer, Mannheim, Germany). HDL cholesterol was measured in the supernatant after precipitation of apolipoprotein B-containing particles with phosphotungstic acid and magnesium ions. LDL cholesterol was calculated with the Friedewald formula [41]. ApoB was evaluated by nephelometric method with a Behring Nephelometer 100 Analyzer (Behring, Marburg, Germany).

### 2.4. Statistical analysis

We reported means ± standard deviation (S.D.) for continuous variables with a normal distribution. For Lp(a) serum levels, the median and interquartile ranges are reported. Because the small size of the observations we applied a two-way repeated-measures analysis of variance (Friedman's test) with one observation per treatment/block combination to rank-transformed data and post hoc comparisons (Wilcoxon rank-sum test) to determine $P$ values, with SAS Software, Version 9.1 (SAS Institute, Cary, NC, USA). The results of statistical inference were adjusted according to Bonferroni inequality. In this analysis we used the $Z$-value corresponding to $0.05/6 = 0.8\%$ for each of the individual comparisons. The threshold of significance was set at $P < 0.05$.

## 3. Results

A total of 52 patients were included in the study. Simvastatin was prescribed in 26 patients and simvastatin plus L-carnitine in 26 patients. The average age was 64.1 ± 9.5 S.D. (62.7 ± 8.74 S.D. for the simvastatin group and 65.4 ± 10.4 S.D. for the simvastatin plus L-carnitine group), 51.9% were men (53.8% for the simvastatin group and 50% for the simvastatin plus L-carnitine group). Table 1 summarizes the baseline characteristics of the subjects enrolled in the study that include age, sex, glycosylated haemoglobin, body mass index (BMI), co-morbid diseases, and pharmacological co-interventions. Tables 2 and 3 summarizes laboratory values at baseline and at the completion of the study (60 days) for the entire population and each treatment group. For all 52 patients, the mean baseline LDL cholesterol serum level was 150.7 mg/dL (3.90 mmol/L), the mean baseline HDL cholesterol serum level was 41.2 mg/dL (1.07 mmol/L), the non-HDL cholesterol serum level was 171.1 mg/dL (4.42 mmol/L), and the median baseline Lp(a) serum level was 39.2 mg/dL (1.40 μmol/L). There was a significant reduction in LDL cholesterol, non-HDL cholesterol, and apoB serum levels within groups (Bonferroni-$P < 0.01$) but not between groups, while no differences were observed within groups and between groups for HDL cholesterol

Table 1
Baseline demographic characteristics of the study patients ($N = 52$)

| Variables | Both groups ($N = 52$) | Simvastatin ($N = 26$) | Simvastatin + L-carnitine ($N = 26$) |
|---|---|---|---|
| Age (years) | 64.1 ± 9.5 | 62.7 ± 8.74 | 65.4 ± 10.4 |
| Sex, no. (%) | | | |
| Men | 27 (51.9) | 14 (53.8) | 13 (50.0) |
| Glycosylated haemoglobin (%) | 7.1 (0.3) | 7.0 (0.3) | 7.3 (0.2) |
| BMI | | | |
| Median score (interquartile range) | 28.5 (25.9–32) | 27.8 (23.5–31) | 29 (24.5–33) |
| Concomitant disease, no. (%) | | | |
| Hypertension | 6 (11.5) | 3 (11.5) | 3 (11.5) |
| Smokers/non-smokers ratio | 18/34 (0.5) | 10/16 (0.6) | 8/18 (0.4) |
| Concurrent medication, no. (%) | | | |
| ACE inhibitors | 5 (9.6) | 2 (7.7) | 3 (11.5) |
| Acetylsalicylic acid | 3 (5.8) | 2 (7.7) | 1 (3.8) |
| Calcium antagonists | 1 (1.9) | 0 (0.0) | 1 (3.8) |
| ARBs | 2 (3.8) | 1 (3.8) | 1 (3.8) |

Values are expressed as mean (S.D.) unless otherwise indicated. BMI, body mass index; ACE, angiotensin-converting enzyme; ARBs, angiotensin I-receptor blockers.

Table 2
Laboratory parameters at baseline and follow-up

| Variables | Both groups ($N=52$) | Simvastatin ($N=26$) | Simvastatin + L-carnitine ($N=26$) | $P$-value |
|---|---|---|---|---|
| Baseline | | | | |
| Total cholesterol (mg/dL) | 232.8 ± 48.0 | 239.9 ± 57.9 | 225.6 ± 35.4 | 0.42 |
| LDL cholesterol (mg/dL) | 150.7 ± 45.5 | 157 ± 54.2 | 144.3 ± 34.6 | 0.44 |
| HDL cholesterol (mg/dL) | 41.2 ± 11.3 | 41.1 ± 12.2 | 41.2 ± 10.7 | 0.99 |
| Non-HDL cholesterol (mg/dL) | 171.1 ± 54.7 | 198.8 ± 56.6 | 143.5 ± 36 | 0.35 |
| Triglycerides (mg/dL) | 199.6 ± 58.9 | 209.7 ± 61.7 | 189.5 ± 55.4 | 0.26 |
| Total cholesterol/HDL cholesterol ratio | 6.0 ± 1.8 | 6.2 ± 2.0 | 4.6 ± 1.4 | 0.63 |
| Apolipoprotein B (mg/dL) | 127.0 ± 27.2 | 129.6 ± 32.8 | 124.4 ± 20.4 | 0.71 |
| Lipoprotein(a) (mg/dL) | | | | |
| Median score (interquartile range) | 39.2 (28.9–52.0) | 36.5 (25.3–49.0) | 41 (34.0–64.0) | 0.94 |
| 60-Days follow-up | | | | |
| Total cholesterol (mg/dL) | 183.7 ± 31.0 | 185.7 ± 38.8 | 181.7 ± 21.1 | 0.98 |
| LDL cholesterol (mg/dL) | 108.1 ± 28.4 | 111.4 ± 35.8 | 104.7 ± 18.4 | 0.60 |
| HDL cholesterol (mg/dL) | 42 ± 12.4 | 42.2 ± 11.5 | 41.8 ± 13.5 | 0.74 |
| Non-HDL cholesterol (mg/dL) | 162.1 ± 37.8 | 184.4 ± 38.1 | 139.8 ± 20.6 | 0.83 |
| Triglycerides (mg/dL) | 166.1 ± 70.0 | 159.7 ± 57.4 | 172.4 ± 81.4 | 0.92 |
| Total cholesterol/HDL cholesterol ratio | 4.7 ± 1.4 | 5.8 ± 1.6 | 4.7 ± 1.5 | 0.89 |
| Apolipoprotein B (mg/dL) | 101.9 ± 20.2 | 103.4 ± 25.5 | 100.4 ± 13.3 | 0.85 |
| Lipoprotein(a) (mg/dL) | | | | |
| Median score (interquartile range) | 40.1 (29.2–57.3) | 40.8 (31.4–55.3) | 37.8 (25.4–58.1) | 0.71 |

Plus–minus values are means ± S.D. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for lipoprotein(a) to micromoles per liter, multiply by 0.0357.

Table 3
Change in laboratory parameters from baseline by groups

| Variables | Both groups ($N=52$) | Simvastatin ($N=26$) | Simvastatin + L-carnitine ($N=26$) | $P$-value |
|---|---|---|---|---|
| Baseline | | | | |
| Total cholesterol (mg/dL) | | | | 0.80 |
| Mean | −49.1 ± 31.2 | −54.2 ± 31.3 | −44 ± 30.7 | |
| Percent | −19.9 | −21.6 | −18.2 | |
| LDL cholesterol (mg/dL) | | | | 0.89 |
| Mean | −42.6 ± 29.3 | −45.6 ± 33.5 | −39.6 ± 24.7 | |
| Percent | −26 | −26.5 | −25.6 | |
| HDL cholesterol (mg/dL) | | | | 0.78 |
| Mean | 0.9 ± 6.8 | 1.1 ± 6.6 | 0.6 ± 7.2 | |
| Percent | 3.2 | 5 | 1.4 | |
| Non-HDL cholesterol (mg/dL) | | | | 0.69 |
| Mean | −50 ± 33.2 | −55.3 ± 34.1 | −44.6 ± 32.2 | |
| Percent | −24.1 | −26.1 | −22.1 | |
| Triglycerides (mg/dL) | | | | 0.56 |
| Mean | −33.5 ± 30.7 | −50 ± 66.6 | −17.1 ± 71.3 | |
| Percent | −12.7 | −18.9 | −6.4 | |
| Total cholesterol/HDL cholesterol ratio | | | | 0.71 |
| Mean | −1.3 ± 1.5 | −1.6 ± 1.6 | −1.1 ± 1.5 | |
| Percent | −19.5 | −22.4 | −16.5 | |
| Apolipoprotein B (mg/dL) | | | | 0.63 |
| Mean | −25.1 ± 20.7 | −26.2 ± 21.9 | −24 ± 19.9 | |
| Percent | −18.4 | −19.1 | −17.7 | |
| Lipoprotein(a) (mg/dL) | | | | 0.005** |
| Median score | 0.8 | 4.9 | −4.4 | |
| Interquartile range | −5.0 to 5.1 | 1.0 to 8.8 | −11.8 to −0.2 | |
| Percent | 2.1 | 12.7 | −13.0 | |

Plus–minus values are means ± S.D. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for lipoprotein(a) to micromoles per liter, multiply by 0.0357.
** The statistical inferences were adjusted according to Bonferroni inequality: Bonferroni-$P<0.05$.

values. Triglycerides serum levels significantly decreased within simvastatin group (Bonferroni-$P < 0.01$) but not within simvastatin plus L-carnitine group and between groups. Moreover, Lp(a) serum levels significantly change from baseline by groups (simvastatin plus L-carnitine group versus simvastatin group) (Bonferroni-$P < 0.05$). In particular, Lp(a) serum levels increase from baseline to 60 days in the simvastatin group alone versus a significant decrease (Bonferroni-$P < 0.05$) in the simvastatin plus L-carnitine group. Both treatments were well tolerated and no adverse events were reported in either group. Finally, no discontinuation of treatment because of an adverse event or the patient's preference or for other reasons, were observed in either groups of treatments.

## 4. Discussion

Our findings provide support for a possible role of L-carnitine in lowering Lp(a) serum levels in patients with type 2 diabetes mellitus. No difference in time by groups (simvastatin and simvastatin plus L-carnitine) were observed in the reduction of LDL cholesterol, non-HDL cholesterol, and apoB serum levels. On the other hand, Lp(a) serum levels increase by time in the simvastatin group alone versus a significant decrease in the simvastatin plus L-carnitine group. No adverse events in both treatments were observed.

Given the strong association of elevated Lp(a) levels with vascular disease (CAD and CVD) and the suggested role of this lipoprotein also in AD, many researchers have examined possible treatments to reduce Lp(a) levels [12–36]. However, in humans, of standard lipid-lowering therapies, only nicotinic acid and its derivatives, acipimox and niceritrol, have been shown to favorably influence Lp(a) levels, but side effects and toxicity prevent the widespread use of nicotinic acid as a Lp(a) lowering agent [26,27], while its analogues have fewer side effects [28–30]. Contradictory findings have been reported concerning variations in Lp(a) levels on statin treatment [16–25]. No significant effect has been demonstrated in most cases [16,21,22], and some studies reported a statin-mediated increase in Lp(a) levels [17–20]. Patients with a normal cholesterolaemia might be more sensitive to the Lp(a) lowering effects of enhanced LDL clearance. In fact, experimental and clinical data suggest that activation of the LDL receptors by the use of statins, in the presence of normal plasma cholesterol levels, may result in a reduction of Lp(a) concentrations [42], but these data were not replicated in other studies [43]. In the present study, Lp(a) serum levels increased although not significantly in the group with simvastatin alone, suggesting that the described effect of L-carnitine in lowering Lp(a) may also well counteract the Lp(a) increasing activity exerted by some statins [17–20]. Given the contrasting findings on the efficacy of statin treatment in lowering Lp(a) levels, various combined treatments with other agents more effective in subjects with hyper-Lp(a) were suggested [29,44,45]. In patients with combined hyperlipidaemia, adding acipimox to simvastatin reduced Lp(a) and substantially but not significantly lowered triglycerides [29], the combination therapy with niceritrol and pravastatin decreased triglyceride and Lp(a) levels and increased HDL cholesterol levels, targets not achieved by administration of pravastatin alone [44]. Furthermore, in heart transplant patients receiving immunosuppressive therapy, both bezafibrate and lovastatin improved the lipid profile, but only bezafibrate decreased plasma Lp(a) levels [45].

In patients with type 2 diabetes mellitus, combined therapy with simvastatin (20 mg/day) and L-carnitine (2 g/day) demonstrated greater lipid-lowering efficacy than simvastatin alone, especially with regard to triglyceride levels [34]. Moreover, in subjects with type 2 diabetes mellitus not on anti-diabetic medications, L-carnitine (2 g/day) significantly lowered the plasma Lp(a) level compared with placebo in selected hypercholesterolemic patients [36]. Given that the risk of developing CAD in patients with high Lp(a) levels and type 2 diabetes mellitus is increased up to three-fold as compared to patients without type 2 diabetes mellitus and with high Lp(a) levels [9], the significant decrease of Lp(a) serum levels within simvastatin plus L-carnitine group and the greater decrease in the simvastatin plus L-carnitine group than in the only simvastatin group, may have clinical significance in diabetic patients. In fact, according to the recent Third Report of the National Cholesterol Education Program (NCEP) on Detection, Evaluation, and Treatment of High Blood Cholesterol (Adult Treatment Panel III—ATP III), diabetes mellitus is considered a CAD risk equivalent [46]. ATP III guidelines suggested an intensive LDL-lowering and a more aggressive management of other coronary risk factors in subjects with a CAD risk equivalent as diabetes mellitus. As noted in our previous study on subjects with a wide range of Lp(a) levels [33] and in a successive double blind placebo controlled trial [35], the reduction in Lp(a) concentrations was not accompanied by a reduction of triglyceridemia. In fact, triglycerides serum levels significantly decreased within simvastatin group but not within simvastatin plus L-carnitine group and between groups. However, in the present study there was a significant reduction in LDL cholesterol, non-HDL cholesterol, and apoB within groups but not between groups.

The mechanisms by which L-carnitine can reduce elevated serum levels of Lp(a) are, at present, unclear. Effective treatments for hyper-Lp(a) levels, besides estrogens/tamoxifene, affecting apo(a) mRNA expression [47], have been with drug reducing fatty acid inflow into the liver cell, e.g. nicotinic acid and derivatives [26–31]. The effect of high dose nicotinic acid is typically exerted on patients with elevated Lp(a) levels (i.e. those most likely to have increased production) [26] and a similar effect is exerted by derivatives as α-tocopherol nicotinate [48]. L-Carnitine plays an important role in the mitochondrial uptake of long-chain fatty acids by facilitating their transportation across the inner mitochondrial membrane to undergo β-oxidation. L-Carnitine also affects glucose metabolism by activating pyruvate dehydrogenase,

thus enhancing the flux of pyruvate into the citric acid cycle [49]. This agent by stimulating fatty acid breakdown at the mitochondrial level [50] could reasonably reduce liver fatty acid inflow for Lp(a) production, thus distinctly lowering levels in the subjects presumably affected by excess production of this atherogenic lipoprotein.

The results of our trial, despite the obvious limitations of the open design, a small number of subjects, and the very short duration, suggest that, in a patient population at high risk of CAD events, such as diabetic patients with hyper-Lp(a), the addition of L-carnitine to a lipid-lowering treatment of proven efficacy, such as simvastatin, may translate into increased clinical benefits in terms of CAD protection. This trial is basically hypothesis generating and further larger trials will be required to determine if the observations are reproducible and if there are any consequential clinical correlates of these findings. This treatment combination offers clinical advantages in terms of the potential synergistic activities of the two compounds and good tolerability, and its role among lipid-lowering strategies aimed at achieving the greatest possible reduction in CAD risk should be further explored.

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