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Effects of Rosuvastatin Versus Atorvastatin, Alone or in Combination, on Lipoprotein (a): A Single-Center Study

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Abstract

Background: There are little evidences about the therapeutic efficacy of different lipid-lowering agents in the reduction of elevated lipoprotein(a) [Lp(a)]. **Objective:** testing the effect of different lipid-lowering agents on elevated Lp(a). **Methods:** prospective interventional study performed in patients with CAD, or high CAD risk, with Lp(a), >50 mg/dL. Lp(a), total cholesterol (C), HDL-C, LDL-C, triglycerides (TGs), apolipoprotein (Apo) A1, Apo B, enzymes of myocyte and hepatic injury were comparatively analyzed between 4 lipid-lowering strategies: rosuvastatin (R group) 40 mg, atorvastatin (A group) 80 mg, atorvastatin 40 mg add-on micronized fenofibrate (A+F group), and atorvastatin 40 mg add-on 1 g extended-release niacin (A+ERN group). Comparison was made for their therapeutic efficacy on Lp(a), and safety. **Results:** 87 patients with mean Lp(a) 94.6 ± 39.6 mg/dL were analyzed. Groups: 25 patients in the R, 22 in the A, 20 in the A+F and 20 in A+ERN group. Significant reduction in all lipid fractions in all treatment groups was reported after 6 months. The average reduction of Lp(a) was 15.9 ± 21.0 mg/dL, with: 18.2 ± 24.8 ($P = 0.001$) in the R group, 17.3 ± 10.4 (P = 0.001) in A+F, 19.5 ± 10.9 (P = 0.001) in A+ERN and the lowest in the A group (11.24 ± 22.91, $P = 0.032$). No adverse effects were observed in any of the treatment groups. **Conclusions:** When compared with atorvastatin, it seems that rosuvastatin can achieve more significant decrease of Lp(a).The efficacy of the second one can be increased by adding fibrate or ERN.

Keywords

dyslipidemia, lipoprotein (a), statins, extended-release niacin (ERN), micronized fenofibrate

Introduction

Lipoprotein (a) [Lp(a)] comprises a low-density lipid fraction and protein component apoprotein (a) [apo(a)]. Lp(a) levels are genetically determined, and remain relatively stable over a lifetime. Elevated Lp(a) is an independent risk factor for coronary artery disease (CAD).[1,2] Mean values of Lp(a) gathered from a Framingham Study cohort were 14 mg/dL for men, and 15 mg/dL for women, with a standard deviation of 17 mg/dL for both genders. Levels above 50 mg/dL are considered elevated.[1,2]

There is a recommendation in the 2011 ESC/EAS Guidelines for the Treatment of Dyslipidemias, for the measurement of Lp(a) in individuals with a strong family history of ischemic heart disease or with premature CAD but not in the general population [class of recommendation IIa, level of evidence (loe) C].[2-4] The European Atherosclerosis Society also recommends screening for elevated Lp(a) in those at intermediate or high cardiovascular disease (CVD)/coronary heart disease risk, with a desirable level of less than 50 mg/dL.[5] Elevated Lp(a) was identified as a risk factor in the 2013 American College of Cardiology/American Heart Association Guidelines on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, but without screening or treatment recommendations.[6]

There is little evidence about the therapeutic efficacy of different lipid-lowering agents in reducing Lp(a). Nicotinic acid (niacin) is one of the first drugs used to treat high Lp(a) that was proven to be effective.[2,7] It was also the only drug recommended by the European Atherosclerosis Society Consensus panel in 2010.[5] In recent years, 2 meta-analyses

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by Takagi and coworkers have been published on the effectiveness of statins in general and rosuvastatin, specifically, in the treatment of elevated Lp(a).[8-10]

Our intent was to evaluate the efficacy of different lipid-lowering agents in lowering Lp(a) levels in the Macedonian population.

The Aim of the Study

The primary aim was to compare the therapeutic efficacy of different statins—rosuvastatin versus atorvastatin alone—in combination with extended-release niacin (ERN) or micronized fenofibrate in lowering increased Lp(a). The secondary aim was to compare their efficacy on other lipoprotein (LP) fractions. We also aimed to compare the safety profile of the prescribed medications, especially when used as a combination therapy.

Material and Methods

This was a prospective, open-label, interventional, single-center study that aimed to compare the efficacy of different lipid-lowering strategies, including: rosuvastatin and atorvastatin, the latter alone and in combination with ERN or micronized fenofibrate. The study was approved by the institutional review board, and all patients gave written informed consent.

Participants were >18 years old with an indication for statin therapy as a result of their primary condition (CAD or high SCORE [Systematic COronary Risk Evaluation] risk) and were also found to have significantly increased level of Lp(a) (>50 mg/dL).

Analyzed Variables

The variables analyzed were age, gender, risk factors for CAD, comorbidities, SCORE risk (for patients without confirmed CAD: http://www.heartscore.org), laboratory parameters (hemogram, blood urea, creatinine, glucose, myoglobin, creatine phosphokinase [CPK], aspartate and alanine transaminase [AST and ALT]), LP fractions (Lp(a), cholesterol [C], triglycerides [TGs], HDL-C, and LDL-C, apolipoprotein [Apo] A1, and Apo B), and medications used (cardiovascular, for associated conditions and lipid lowering).

Patients were randomly assigned to 1 of 4 treatment regimens: rosuvastatin group (R), initial dose of 20 mg was uptitrated to 40 mg on the first control visit (8-12 weeks) if no adverse effects were reported; atorvastatin group (A); atorvastatin add-on micronized fenofibrate group (A+F); and atorvastatin add-on ERN group (A+ERN). For atorvastatin, the initial dose was 40 mg, and on the first control visit (8-12 weeks), if no adverse effects occurred, patients were either uptitrated to 80 mg or 145 mg micronized fenofibrate or 1 g ERN was added (decision made on patients' preference). The patients remained on the same treatment regimen for 6 months.

The major exclusion criteria were CPK ≥3× upper limit of normal (ULN), ALT ≥1.5× ULN, AST ≥1.5× ULN, calculated creatinine clearance <30 mL/min, hemoglobin A_{1C} (A1C) ≥9%, persistent uncontrolled hypertension (on triple antihypertensive therapy without achieved arterial hypertension treatment targets), and pregnancy and lactation.

Data were collected from medical history, clinical examination, and blood sampling. Blood sampling was repeated on an 8- to 12-week basis during the treatment period. Methods used for LP fraction determination are described in the appendix. Comparison was made between the 4 treatment regimens as regards their therapeutic efficacy and safety profile.

Statistical Analysis

Descriptive statistics were in terms of absolute values, percentages, and means ± SD. Comparative statistics were in terms of the χ^2 test, odds ratios (ORs; with CI), *t*-test, and ANOVA (with the post hoc Tukey test). Significance was determined at a level of <0.05.

Results

We screened 250 patients with dyslipidemia, 87 of whom met the criterion of Lp(a) >50 mg/dL and were enrolled in the study. The mean age of the patients was 61.0 ± 12.1 years, and men predominated (56.3%); 56.9% of the patients had CAD, others were with high CVD risk. Overweight and/or obesity (64.4%) and hypertension (64.4%) were the predominant risk factors. Only 18.3% had diabetes. Men had an OR = 5.1 for smoking and 2.8 for CAD as compared with women, whereas women had higher SCORE risk. Lp(a) ranged from 52 to 183 mg/dL (mean = 94.63 ± 39.55 mg/dL), with men having higher levels but without statistical significance (Table 1). Comparative gender analysis of LP fractions revealed that women had significantly higher total C and LDL-C.

Patients were divided into 4 groups of treatment. There were no significant differences in the levels of the LP fractions between the groups at the beginning of the treatment (Table 2).

Therapeutic Efficacy

The primary outcome of interest was Lp(a). Statistically significant reduction of Lp(a) was observed in all treatment groups (Table 3). The reduction was similar in R, A+E, and A+ERN groups ($P = 0.001$). The lowest mean reduction rate was observed in group A ($P = 0.032$). However, at the end of the treatment period, only 16.9% of all patients

Table 1. Baseline Characteristics of the Patients.[a]

Variable	Total, n (%) of Total	Men, n (%)	Women, n (%)	Significance (*P*)
Gender	87	49 (56.3%)	38 (43.7%)	
Age (years)	61.0 ± 12.1	61.5 ± 11.0	62.7 ± 12.7	ns
BMI (kg/m^2)	27.2 ± 3.9	26.9 ± 3.7	28.3 ± 4.4	ns
Normal weight (19.9-24.9)	31 (35.6%)	20 (40.8%)	11 (28.9%)	
Overweight (25-29.9)	36 (41.4%)	16 (32.6%)	20 (52.6%)	ns
Obese >30	20 (23.0%)	13 (26.6%)	7 (18.5%)	
Smoking	23 (26.4%)	19 (38.8%)	4 (10.5%)	0.013 (OR/M = 5.1; CI = 1.3-19.9)
Diabetes mellitus	16 (18.4%)	11 (22.4%)	5 (13.1%)	ns (OR/M = 1.6; CI = 0.6-6.4)
HTA	56 (64.4%)	34 (69.4%)	22 (57.9%)	ns (OR/M = 1.4; CI = 0.7-2.7)
Comorbidities				
CAD patients	49 (56.3%)	34 (69.4%)	15 (39.5%)	0.041 (OR/M = 2.8; CI = 1.0-7.7)
SCORE risk	38 (43.7%)	15 (30.6%)	23 (60.5%)	
Mean SCORE risk	8.2 ± 4.1	6.7 ± 3.3	10.5 ± 4.2	0.010
High SCORE risk, n	28 (32.2%)	12 (24.5%)	16 (42.1%)	0.050
Very high SCORE risk, n	10 (11.5%)	3 (6.1%)	7 (18.4%)	
Medications				
ACE inhibitor	60 (69.0%)	35 (71.4%)	25 (65.8%)	ns
ARBs	16 (18.4%)	12 (24.5%)	4 (10.2%)	ns
Diuretics	33 (37.9%)	19 (39.6%)	14 (36.8%)	ns
MRA	10 (11.5%)	10 (20.4%)	0 (0%)	0.008 (OR/M = 4.05; CI = 0.1-6.9)
BB	56 (64.4%)	32 (65.3%)	24 (63.1%)	ns
CCB	25 (28.7%)	15 (30.6%)	10 (26.3%)	ns
Antiplatelets	74 (85.0%)	45 (91.8%)	29 (74.3%)	ns
OAK	8 (9.2%)	4 (8.2%)	4 (10.5%)	ns
DM treatment				
Insulin	4 (4.6%)	4 (8.2%)	0	
OH	7 (8.0%)	3 (6.1%)	4 (10.5%)	ns
OH+Insulin	5 (5.7%)	4 (8.2%)	1 (2.6%)	
Lipoprotein fraction (mg/dL)				
C	220.4 ± 42.9	206.9 ± 32.9	238.6 ± 47.9	0.002
TG	219.7 ± 116.0	202.8 ± 84.1	240.9 ± 146.1	ns
LDL-C	146.9 ± 27.1	136.5 ± 18.2	160.9 ± 30.9	0.000
HDL-C	44.8 ± 10.4	46.0 ± 9.7	43.3 ± 10.8	ns
Apo A1	144 ± 27	144 ± 29	144 ± 26	ns
Apo B	93 ± 28	88 ± 19	99 ± 36	ns
Lp(a)	94.63 ± 39.55	99.91 ± 40.88	87.61 ± 37.3	ns

Abbreviations: ACE, angiotensin-converting enzyme; Apo, apolipoprotein; ARB, angiotensin receptor blocker; ASA, aspirin; BB, β-blockers; BMI, body mass index; C, cholesterol; CAD, coronary artery disease; CCB, calcium channel blocker; DM, diabetes mellitus; F, females; HDL-C, high-density lipoprotein cholesterol; HTA, arterial hypertension; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); M, males; MRA, mineralocorticoid receptor antagonist; OAK, oral anticoagulant medication; OH, oral hypoglycemic medications; OR, odds ratio; SCORE, Systematic COronary Risk Evaluation; TG, triglycerides.

[a]Only values with statistical significance ($P < 0.05$) are expressed as numbers. The results are shown as means with SDs, percentages, and as odds ratios with CIs.

reached the target value of <50 mg/dL Lp(a) without significant intertreatment differences.

Regarding efficacy on other LP fractions, all treatments were equally potent in the reduction of total C, LDL-C, and TG. The effect on HDL-C varied between different treatments. The most significant increase was observed in the rosuvastatin group, followed by atorvastatin and A+ERN groups, but none was observed in the A+F group. Both statins were equally effective in increasing Apo A1 and decreasing Apo B, whereas the combination therapy proved ineffective.

Safety

During the treatment period, no major adverse effects were reported in any of the treatment groups. No flushing or muscle pain was reported by the patients, and no

Table 2. Distribution of the Patients in Accordance With the Antilipemic Treatment and Lipoprotein Levels at Study Entrance.[a]

Treatment Groups (%)	C (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	TG (mg/dL)	Apo A1 (mg/dL)	Apo B (mg/dL)	Lp(a) (mg/dL)
R (29%)	209.98 ± 39.06	44.47 ± 8.89	144.62 ± 20.88	208.15 ± 96.54	144 ± 21	93 ± 31	95.67 ± 35.95
A (25%)	238.98 ± 42.92	44.47 ± 10.83	153.52 ± 29.39	215.23 ± 62.89	147 ± 26	99 ± 28	97.35 ± 50.32
A+F (23%)	213.07 ± 45.24	44.08 ± 14.69	143.08 ± 32.48	186.89 ± 115.94	133 ± 42	93 ± 17	87.07 ± 13.89
A+N (23%)	212.68 ± 42.54	47.56 ± 9.67	142.30 ± 34.03	295.84 ± 156.77	148 ± 32	75 ± 21	92.59 ± 41.32
Total (100%)	220.42 ± 42.92	44.86 ± 10.44	146.94 ± 27.07	219.66 ± 116.03	144 ± 27	93 ± 28	94.63 ± 39.55
ANOVA significance	ns	ns	ns	ns	ns	ns	ns

Abbreviations: A, atorvastatin; A+F, atorvastatin add-on micronized fenofibrate group; A+ERN, atorvastatin add-on extended-release niacin group; Apo, apolipoprotein; C, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); R, rosuvastatin; TG, triglycerides.
[a]The results are shown as mean values with SDs. Treatment groups are shown as percentages of total number.

Table 3. Mean Values of Lipoprotein (LP) Fractions at the Beginning and End of Treatment as a Function of Antilipemic Treatment.[a]

	Treatment				
LP Fraction	Rosuvastatin (R)	Atorvastatin (A)	Atorvastatin Add-on Fibrate (A+F)	Atorvastatin Add-on Niacin (A+ERN)	Total
Lp(a) I[b]	95.67 ± 35.95	97.35 ± 50.32	87.07 ± 13.89	92.59 ± 41.32	94.63 ± 39.55
Lp(a) II[c]	77.47 ± 34.11	86.11 ± 42.25	69.73 ± 20.33	73.06 ± 32.62	77.25 ± 36.08
Delta Lp(a)	18.20 ± 24.77	11.24 ± 22.91	17.34 ± 10.36	19.54 ± 10.86	17.32 ± 34.06
Significance (*P*)	0.001	0.032	0.001	0.001	0.001
C I[b]	209.98 ± 39.05	238.98 ± 42.92	213.07 ± 45.24	212.68 ± 42.54	183.35 ± 42.92
C II[c]	157.38 ± 31.71	183.29 ± 38.67	165.51 ± 24.36	156.99 ± 40.22	154.68 ± 36.74
Delta C	52.59 ± 33.25	55.68 ± 32.09	47.56 ± 32.48	34.80 ± 35.58	28.55 ± 38.52
Significance (*P*)	0.000	0.000	0.002	0.020	0.000
HDL-C I[b]	44.47 ± 8.89	44.47 ± 10.83	44.08 ± 14.69	47.56 ± 9.67	44.86 ± 10.44
HDL-C II[c]	48.34 ± 10.05	49.88 ± 14.69	49.11 ± 10.44	62.64 ± 19.72	49.49 ± 12.76
Delta HDL-C	3.87 ± 5.03	5.41 ± 10.05	4.64 ± 7.35	15.08 ± 16.63	4.63 ± 11.26
Significance (*P*)	0.001	0.021	0.93(ns)	0.027	0.000
LDL-C I[b]	144.62 ± 20.88	153.52 ± 29.39	143.08 ± 32.48	142.30 ± 34.02	146.94 ± 27.07
LDL-C II[c]	94.35 ± 28.23	114.46 ± 35.19	105.57 ± 17.01	100.93 ± 33.25	98.99 ± 28.23
Delta LDL-C	50.27 ± 20.88	39.05 ± 30.93	37.51 ± 30.55	41.38 ± 24.36	46.96 ± 30.23
Significance (*P*)	0.000	0.000	0.007	0.001	0.000
TG I[b]	208.15 ± 96.54	215.23 ± 62.89	186.89 ± 15.94	285.84 ± 245.35	219.66 ± 116.03
TG II[c]	137.29 ± 65.54	133.75 ± 52.26	99.20 ± 15.05	178.03 ± 136.40	147.03 ± 116.92
Delta TG	70.86 ± 69.09	79.71 ± 61.11	87.69 ± 20.37	117.80 ± 116.03	71.66 ± 98.91
Significance (*P*)	0.000	0.000	0.000	0.016	0.003
Apo A1 I[b]	144 ± 21	147 ± 26	133 ± 42	148 ± 32	144 ± 27
Apo A1 II[c]	156 ± 24	156 ± 27	149 ± 23	152 ± 27	155 ± 24
Delta Apo A1	12 ± 22	09 ± 15	15 ± 25	50 ± 11	12 ± 29
Significance (*P*)	0.014	0.011	0.100 (ns)	0.224 (ns)	0.032
Apo B I[b]	93 ± 31	99 ± 28	93 ± 17	75 ± 21	93 ± 28
Apo B II[c]	78 ± 23	86 ± 26	82 ± 16	76 ± 22	82 ± 24
Delta Apo B	15 ± 19	13 ± 18	11 ± 24	01 ± 09	10 ± 14
Significance (*P*)	0.001	0.004	0.201 (ns)	0.835 (ns)	0.002

Abbreviations: Apo, apolipoprotein; C, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); TG, triglycerides.
[a]The results are shown as mean values with standard deviations.
[b]I: values at the beginning.
[c]II: values at the end of the treatment period.

Table 4. Safety Profile (Effect on Liver and Skeletal Muscle, Expressed Through Markers of Hepatic Cell and Skeletal Muscle Cell Injury) as a Function of Antilipemic Treatment.[a]

Treatment	Beginning (I)/End (II)	Myoglobin (μg/L)	CPK (μkat/L)	AST (μkat/L)	ALT (μkat/L)
Rosuvastatin	I	2.17 ± 0.51	1.28 ± 0.76	0.55 ± 0.35	0.65 ± 0.49
	II	2.63 ± 1.31	1.34 ± 0.63	0.37 ± 0.18	0.42 ± 1 = 0.17
Atorvastatin	I	2.16 ± 0.85	1.41 ± 0.83	0.39 ± 0.16	0.62 ± 0.39
	II	2.11 ± 0.51	1.47 ± 0.76	0.30 ± 0.12	0.40 ± 0.13
Atorvastatin + Fenofibrate	I	2.68 ± 0.34	1.71 ± 0.29	0.32 ± 0.18	0.40 ± 0.21
	II	2.11 ± 0.85	1.73 ± 1.08	0.35 ± 0.13	0.38 ± 0.20
Atorvastatin + ERN	I	2.11 ± 0.22	1.63 ± 0.97	0.64 ± 0.25	0.84 ± 0.55
	II	2.56 ± 0.86	1.65 ± 0.49	0.34 ± 0.08	0.39 ± 0.19
ANOVA significance (*P*)		ns	ns	ns	ns

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ERN, extended-release niacin.
[a]The results are shown as mean values with standard deviations.

significant increase in skeletal or hepatic enzymes was observed (Table 4).

Discussion

Clinical Significance of Lp(a)

Lp(a) is a well-known risk factor for atherosclerosis, with a linear correlation between Lp(a) values and CVD risk. The risk associated with elevated Lp(a) is reported to be higher in women (Shai et al, from the Nurses' Health Study).[2] The Copenhagen City Heart Study reports a stepwise increase in the risk of myocardial infarction with increasing levels of Lp(a), which is similar in both genders. Similar results were found in a meta-analysis of 12 prospective studies performed by Craig and coauthors, The Reykjavik Study, The Bruneck Study, The ARIC study, and The PRIME Study.[2,3] However, up to date, there is no clear evidence of the therapeutic efficacy of lipid-lowering agents on Lp(a). Also, there is a lack of evidence that Lp(a) lowering will result in cardiovascular risk reduction.[1,2,4] Our study aimed to test the effect of different therapeutic treatment strategies on elevated Lp(a) levels. We selected a group of patients with very high Lp(a) levels (94.6 ± 39.6 mg/dL; Table 1).

Screening and Treatment Targets for Lp(a)

Currently, Lp(a) measurement is recommended for people with high CAD risk, premature CV events, or a strong familial history of premature CAD.[4,5] These were the characteristics of our population (Table 1). The recommendation from EAS is that Lp(a) levels should be ≤50 mg/dL.[5] But Lp(a) levels are genetically determined and remain constant throughout the lifetime; also, data show that current therapies are unable to reduce elevated Lp(a) to an acceptable level.[11] This was the case in our study as well. Significant reduction was observed with all treatments, with a mean reduction of the Lp(a) level after treatment to 77.25 ± 36.08 mg/dL ($P = 0.001$), although only 16.9% of patients achieved the target level of <50 mg/dL during the treatment period.

Treatment Strategies: Role of Lipid-Lowering Agents in Elevated Lp(a) Treatment

Several lipid-lowering agents are reported to effectively decrease the Lp(a) levels, among them niacin, fibrates and statins.[2,12-14]

Niacin. Niacin was among the first lipid-lowering agents proven to be effective in Lp(a) treatment, with a possible decrease of Lp(a) by ~20% to 30%. Until a few years ago, it was considered to be the best drug option, with a disadvantage of requiring very high doses, as reported by Carlson (4 g/d), which were associated with many adverse effects. The ER formulation was used in doses of 1 to 3 g/d, with significantly reduced adverse effects.[7] Pan et al[15] reported that ERN is effective in Lp(a) reduction even in the treatment of diabetic dyslipidemias, independently of A1C levels. In the COMPELL study, where 4 treatment regiments were tested, the statin/ERN combination lead to an ~40% reduction of Lp(a), with negligible adverse effects.[16] Effective Lp(a) lowering may be dependent on the type of lipid abnormalities associated with high Lp(a), the dose of niacin, type of formulation, time of treatment, and so on. [2,7,12,13,15] The effect of niacin on cardiovascular outcomes is uncertain. The HPS2-THRIVE trial found an increased risk of myopathy, diabetes, and increased ALT, without CVD risk reduction, when 2 g of ERN/LRPT (Laropiprant) were added to statin therapy, despite its beneficial effect on LP fractions (Lp(a) was not a subject of analysis in this study).[17]

In our study, the A+ERN group was associated with the highest mean reduction in Lp(a) (19.54 ± 10.86 mg/dL),

with the same statistical significance as rosuvastatin and A+F treatments ($P = 0.001$). Efficacy on total C, LDL-C, HDL-C, and TG was somewhat smaller than with statin monotherapy and inferior for Apo A1 and Apo B (Table 3). Patients did not develop any adverse effects (but it may be because of the low 1-g/d dosage as well as the fact that it was not a combination of ERN/LRPT, a combination that could have been the cause of the adverse reactions reported in HPS2-THRIVE).[17]

Fenofibrate. Fibrates also demonstrated some Lp(a)-lowering effects, but no large-scale trials evaluating fenofibrates and Lp(a) have been published.[2] Markel[7] reports that several studies have demonstrated antiatherosclerotic action for both niacin and fibrates. But, in the ACCORD trial lipid arm, intensive lipid-lowering treatment with combined statin-fibrate therapy did not lead to reduction in CV events. So despite the fact that fibrates are effective in reduction of sdLDL (Small Dense LDL) particles, it does not necessarily translate to CVD risk reduction.[18]

In our study, we found that A+F treatment led to a significant decrease of Lp(a) (17.34 ± 10.36; $P = 0.001$), similar to the R and A+ERN treatments. It was also effective in TG and LDL-C lowering, but not in the lowering of other LP fractions (Table 3).

Statins. The effects of statins on Lp(a) levels are variable, especially depending on the statin that is used. Plenge reported that simvastatin moderately increases Lp(a) in individuals with increased C. In the COMPELL study, atorvastatin led to modest but significant reductions in Lp(a).[14] Gonbert et al[19] also reported similar findings. In the REGRESS Study, pravastatin therapy had a small effect on Lp(a). In the JUPITER Trial, a small but statistically significant decrease of Lp(a) was observed with rosuvastatin.[2,8-10] Takagi and coworkers[8,10] conducted the first meta-analysis of the effect of statins on Lp(a), reporting that statins do have a favorable effect on Lp(a), with rosuvastatin being the most potent among them.

In our study, a more favorable effect across all LP fractions was observed with rosuvastatin in comparison to atorvastatin. The former led to a more pronounced effect on Lp(a). This can be a result of their pharmacokinetic differences (hydrosolubility vs liposolubility, less dependence of rosuvastatin on circulating transport proteins, hepatic enzyme activation, etc).

Limitations of the Study

One limitation is the small sample size (the results might have been different if we had had a larger study population). The low dose of ERN used (1 g) might influence study results, although some of the clinical trials reported a dosage in the range of 0.5 to 2 g. We would like to emphasize that the aim of our study was not to determine the clinical effects of Lp(a) lowering, given the fact that a study like that would mean a follow-up period of at least several years.

Learning Points

According to our results, statins alone, or in combination with fibrates or ERN, can decrease Lp(a), with rosuvastatin demonstrating higher statistical significance in comparison to atorvastatin when used as monotherapy. However, even more important is the finding that in patients with significantly increased levels of Lp(a), it is very difficult to achieve a target level of <50 mg/dL, no matter which lipid-lowering agent is used and what dosage regimen is followed.

Conclusion

When compared with atorvastatin, it seems that rosuvastatin can achieve a more significant decrease of Lp(a). While equally effective in optimizing total C, LDL-C, TG, Apo A1, and Apo B, rosuvastatin was also found to be more effective in increasing HDL-C. Efficacy of atorvastatin on the Lp(a) can be increased by adding either fibrate or ERN, but adding these agents has no benefit on optimization of Apos. Effect on HDL-C differs between fibrate and ERN (when added to statin therapy), with the latter demonstrating a significant increase of HDL-C. Used in recommended doses, even as a combination therapy, these medications were shown to be well tolerated and free of major adverse effects.

Appendix

Methods to Determine LP Fractions: Determination of Lipid and LP Components

Determination of Total C Concentration in Serum or Plasma. Total cholesterol was measured enzymatically in serum or plasma in a series of coupled reactions that hydrolyze cholesterol esters and oxidize the 3-OH group of cholesterol. One of the reaction byproducts, H_2O_2 was measured quantitatively in a peroxidase catalyzed reaction that produces a color. Absorbance was measured at 500 nm. The color intensity is proportional to cholesterol concentration.

Determination of TGs in Serum or Plasma. TGs in serum or plasma were also measured using enzymatic methods using a series of coupled reactions in which TGs were hydrolyzed to produce glycerol. Glycerol is then oxidized using glycerol oxidase, and H_2O_2, one of the reaction products, was measured as described above for total cholesterol. Absorbance is measured at 500 nm.

Determination of HDL-C Concentration in Serum or Plasma. The HDL measurement was done directly in serum. The basic

principle of the method is as follows: the Apo B–containing LPs in the specimen were reacted with a blocking reagent that renders them nonreactive with the enzymatic cholesterol reagent under conditions of the assay. The Apo B–containing LPs were, thus, effectively excluded from the assay, and only HDL-C is detected under the assay conditions. This reaction results in a colored solution, whose absorbance is measured at 600 nm.

Determination of LDL-C Concentration in Serum or Plasma. Concentration of LDL cholesterol was estimated using the direct colorimetric method based on a combination of sugar compounds with detergents. These mixtures enable selective determination of LDL, with end reaction that includes peroxidase and results in blue quinoneimine. Intensity and increase of absorbance is measured at 583 nm and is proportional to LDL-C concentration.

Determination of Apo A and Apo B in Serum or Plasma. Determination of Apo A1 as well as Apo B was based on the immunoturbidimetric principle during which Apo A1/Apo B is precipitate with specific antiserum and measured turbid metrically at 340 nm.

Determination of Lp(a) in Serum or Plasma. Immunoturbidimetric method enhanced by particle was used in determination of this Lp(a). LPs from serum agglutinate with latex particles coated with specific anti-Lp(a) antibody. Formed precipitate is turbid metrically measured at 552 nm.

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Declaration of Conflicting Interests

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