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The effects of atorvastatin 30 mg compared with atorvastatin 40 mg in patients with primary hyperlipidemia: a multicenter study

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Abstract

Introduction: The effective management of high-risk patients requires treatment with high-intensity statins, such as high-dose atorvastatin. However, intensive hypolipidemic treatment is associated with increased incidence of adverse effects, higher financial costs and higher rates of treatment discontinuation. In our country, a novel atorvastatin dosage formulation (30 mg) has been introduced. However, there are no data available on efficacy and safety of this formulation.

Aim: To compare atorvastatin 30 mg/day with atorvastatin 40 mg/day on lipid profile and metabolic parameters in an observational, open label study.

Methods: In this multicenter study, high-risk patients whose low-density lipoprotein cholesterol (LDL-C) levels were above treatment thresholds were included. Patients were randomized to receive atorvastatin 30 mg/day (A30) or atorvastatin 40 mg/day (A40). After 3 months of treatment

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subjects were re-evaluated.
Results: Patients (n=141; 75 males; age 56 years) had a comparable lipid profile at baseline (p = NS between groups). Similar changes in serum lipid parameters were observed in the two study groups. Specifically, LDL-C decreased by 42.1% in the A30 group compared with 44.1% in the A40 group (p=NS). There were no significant changes in carbohydrate homeostasis parameters in any group. Treatment was equally well tolerated in both groups.
Conclusions: Atorvastatin 30 mg resulted in a similar reduction of LDL-C compared with atorvastatin 40 mg.

Key words: Atorvastatin; lipidemic profile; carbohydrate metabolism; side effects

1. Introduction

Hypercholesterolemia is an independent risk factor for the development and progression of cardiovascular disease (CVD), which is the leading cause of global mortality [1]. Statins are the cornerstone of hypercholesterolemia treatment. Indeed, a plethora of studies have shown that statin treatment, by lowering low-density lipoprotein cholesterol (LDL-C), significantly reduces cardiovascular morbidity and mortality [2]. Among statins, atorvastatin is effective and safe with numerous studies attesting its efficacy in both primary and secondary CVD prevention [3-6]. Current guidelines for the management of high and very high CVD risk patients set an aggressive lipid lowering target of decreasing LDL-C<100 and <70 mg/dL, respectively [7]. Moreover, a decrease of LDL-C levels by at least 50% from baseline is recommended [8]. In this context, the use of a high intensity statin such as atorvastatin 40-80 mg is required. However, aggressive lipid-lowering therapy with statins is associated with increased side effects, higher financial cost and higher discontinuation rates [9].

In Greece, a novel atorvastatin formulation of 30 mg has been recently introduced. Studies have shown that the atorvastatin-mediated decrease of LDL-C is linear and dose-depended [10]. Therefore, the LDL-C lowering efficacy of atorvastatin 30 mg/day is expected to be between that of atorvastatin 20 and 40 mg/day. However, there are currently no clinical data regarding the efficacy and safety of atorvastatin 30 mg/day. Atorvastatin 30 mg/day may be associated with a clinically non-significant difference in efficacy compared with atorvastatin 40 mg/day. In addition, the lower dose of atorvastatin may be associated with better safety profile and compliance.

The current study for the first time evaluated the effects of atorvastatin 30 mg/day compared with atorvastatin 40 mg/day on lipid and metabolic profile as well as safety parameters in high-risk patients.

2. Subjects and Methods

a. Subjects

Adult patients at high CVD risk were randomized to receive atorvastatin at doses of 30 or 40 mg/day. Any additional treatment remained unchanged during the study's 3-month observation period. Patients were excluded if they had any of the following: (1) receiving lipid-lowering treatment in the last 3 months prior to recruitment, (2) elevated triglycerides (TGs) (>400 mg/dL), (3) renal disease [estimated glomerular filtration rate (eGFR)<30 mL/min/1.73 m^2], (4) hypothyroidism [thyroid stimulating hormone (TSH) >5 IU/mL], (5) liver dysfunction [lipid function tests> 3 times the upper limits of normal (ULN)], (6) heart failure, (7) no sufficient contraceptive measures in females, (8) history of malignancy, (9) uncontrolled diabetes (glycated hemoglobin >9%),and (10) history of

Table 1: **Baseline demographic characteristics of study participants***

Characteristic		Atorvastatin 30 mg/day	Atorvastatin 40 mg/day	p
N (females/males)		33/37	33/38	NS
Age (years)		54 ± 13	57 ± 13	NS
Body mass index (kg/m²)		29.6 ± 5.4	28.6 ± 5.4	NS
Hypertension (%)		42.4	53.8	NS
Type 2 diabetes mellitus (%)		23.7	25.6	NS
	Never	66.1	53.8	NS
Smoking status (%)	**Current**	22.0	30.8	NS
	Former	11.9	15.4	NS

NS: not significant
**Values are expressed as mean ± SD*

myopathy (myalgias or creatinine kinase >5 times ULN). All participants gave written informed consent and the study protocol was approved by each site's institutional ethics committee.

b. Study design

This study was performed at the following sites: i) the Outpatient Lipid Clinic of the University Hospital of Ioannina, ii) the Outpatient Diabetic Clinic of the "Laiko" Hospital of Athens, iii) the Outpatient Hypertension Clinic of the "Papageorgiou" Hospital of Thessaloniki and iv) the Outpatient Lipid Clinic of the "Tzaneio" Hospital of Piraeus.

This was an open label, observational study. High-risk patients, whose LDL-C levels were above treatment thresholds, were randomly allocated to open-label: i) atorvastatin 30 mg/day (A30 group) or ii) atorvastatin 40 mg/day (A40 group). At baseline and after 12 weeks of treatment demographic, metabolic and safety parameters were assessed. All laboratory determinations were carried out after an overnight fast and performed blindly with regard to treatment allocation. HOmeostasis Model Assessment Insulin Resistance (HOMA-IR) index was calculated as follows: HOMA-IR= fasting insulin (mU/L) × fasting glucose (mg/dL)/405 [11]. Compliance with study medication was assessed at week 24; patients were considered compliant if they took 80%-100% of the prescribed number of tablets.

c. Endpoints

The primary endpoint was the difference of LDL-C change between the two groups after 3 months of treatment. Secondary endpoints included: a) differences in the changes of total cholesterol (TCHOL), non-high-density lipoprotein cholesterol (non-HDL-C), TGs and HDL-C between the two groups, b) differences in the changes of carbohydrate metabolism parameters (glucose, glycated hemoglobin, HOMA-IR) between groups, c) difference of changes of safety metabolic parameters (serum creatinine, creatinine kinase and liver functions tests) as well as myalgia report rates between groups and d) difference in treatment compliance between groups.

d. Statistical analysis

Power analysis showed that a sample size of 70 patients per group would give a 90% power to detect a 3% difference of LDL-C change between the two groups at an α-level <0.05. Values are given as mean

Table 2: **Metabolic parameters at baseline and after 3 months of treatment***

	Baseline*	3 months*	Percentage change
Total cholesterol (mg/dL)			
A30 Group	251 ± 38	171 ± 24	-31.5%†
A40 Group	268 ± 37	176 ± 27	-34.5%†
Triglycerides (mg/dL)			
A30 Group	125 (93-178)	101 (83-133)	-19.3%†
A40 Group	147 (120-201)	111 (78-158)	-24.5%†
HDL-C (mg/dL)			
A30 Group	52 ± 14	50 ± 15	-3.7%
A40 Group	51 ± 12	49 ± 10	-3.3%
LDL-C (mg/dL)			
A30 Group	170 ± 37	98 ± 21	-42.1%†
A40 Group	182 ± 35	102 ± 25	-44.1%†
Non-HDL-C (mg/dL)			
A30 Group	186 ± 39	124 ± 25	-33.3%†
A40 Group	198 ± 48	128 ± 31	-35.4%†
Apolipoprotein AI (mg/dL)			
A30 Group	154 ± 25	161 ± 35	+3.9%
A40 Group	153 ±24	154 ± 8	+0.3%
Apolipoprotein B (mg/dL)			
A30 Group	124 ± 30	74 ± 13	-40.2%†
A40 Group	135 ± 20	75 ± 34	-44.3%†
Lipoprotein (a) (mg/dL)			
A30 Group	11 (5 - 18)	11 (6 - 19)	0.0%
A40 Group	10 (5- 15)	10 (6 - 19)	0.0%
Glucose (mg/dL)			
A30 Group	105 ± 30	106 ± 24	0.0%
A40 Group	105 ± 33	107 ± 20	0.0%

A30: Atorvastatin 30 mg/day, A40: Atorvastatin 40 mg/day HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol

**Values are expressed as mean SD [except for triglycerides and Lp(a) that are expressed as median (interquartile range)]*

†p<0.001 vs. baseline

p=NS for all comparisons between groups

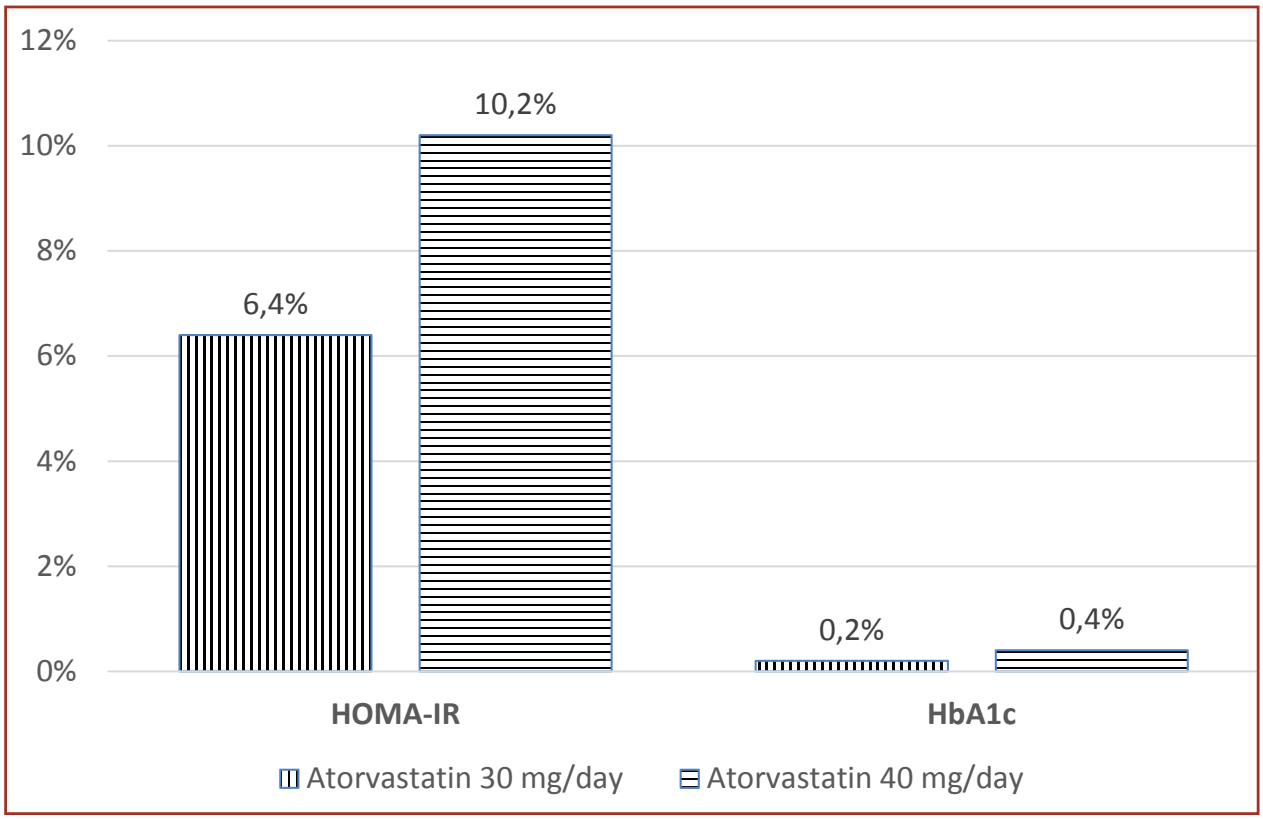

Figure 1: *Percentage change in carbohydrate parameters after 3 months of treatment in a random subgroup of non-diabetic patients in group A30 (n=25) and group A40 (n=25).*
p=NS for all comparisons between groups

± standard deviation (SD) and median (interquartile range) for parametric and non-parametric data, respectively. Continuous variables were tested for lack of normality by the Kolmogorov-Smirnov test and logarithmic transformations were accordingly performed for non-parametric variables. The paired-sample t-test was used for assessing the effect of treatment in each group. Chi^2-tests were performed for categorical variables. Analysis of covariance (ANCOVA), adjusted for baseline values, was used for comparisons between treatment groups. Analyses were performed using the Statistical Package for the Social Sciences (SPSS) 21.0 (SPSS Inc, Chicago, IL).

3. Results

A total of 70 patients (37 males, mean age 54 years old) were enrolled in the A30 group and 71 patients (38 males, mean age 57 years old) were enrolled in the A40 group. No significant differences regarding baseline demographic characteristics were found between the two groups (**Table 1**). Moreover, both groups had similar baseline metabolic profile with no significant differences between them (**Table 2**).

After study end, a comparable decrease of LDL-C was observed in both groups as shown in Table 2 (A30: 42.1% and A40: 44.1%; p<0.001 vs baseline; p=NS between groups). Moreover, a similar decrease of TCHOL, non-HDL-C, TGs and apolipoprotein B levels versus baseline was observed in the A30 and A40 groups as described in Table 2. On the other hand, levels of HDL-C, apolipoproteinAI and lipoprotein (a) remained unchanged in both groups (**Table 2**). No significant differences in the changes of lipid parameters between groups was observed.

Table 3: Serum safety parameters at baseline and after 3 months of treatment

	Baseline*	3 months*
Serum creatinine (mg/dL)		
A30 Group	0.8 ± 0.1	0.8 ± 0.1
A40 Group	0.9 ± 0.2	0.9 ± 0.2
AST (IU/L)		
A30 Group	20 ± 7	24 ± 9
A40 Group	22 ± 10	24 ± 9
ALT (IU/L)		
A30 Group	25 ± 11	28 ± 11
A40 Group	26 ± 12	26 ± 9
γGT (IU/L)		
A30 Group	24 (17-44)	20 (15-38)
A40 Group	20 (15-31)	21 (16-38)
ALP (IU/L)		
A30 Group	71 ± 18	72 ± 21
A40 Group	67 ± 23	73 ± 34
CK (IU/L)		
A30 Group	107 ± 57	121 ± 56
A40 Group	108 ± 62	119 ± 66
Symptoms of myalgia (%)		
A30 Group		0.0%
A40 Group		1.4%

A30: Atorvastatin 30 mg/day, A40: Atorvastatin 40 mg/day

**Values are expressed as mean ± SD [except for γGT that is expressed as median (interquartile range)]*

ALT: alanine aminotransferase, AST: aspartate aminotransferase, γGT: gamma-glutamyltranspeptidase, ALP: alkaline phosphatase

Levels of fasting plasma glucose did not significantly change in any group (**Table 2**). For a random subgroup of non-diabetic patients (n=25 in A30 and n=25 in A40) data on HOMA-IR index and HbA1c were available (**Figure 1**). Levels of HOMA-IR as well as HbA1c did not significantly change both versus baseline and between the two groups. However, a numerical smaller increase of the HOMA-IR index and HbA1c was observed in the A30 group (**Figure 1**).

Both treatments were equally well tolerated and no significant changes in serum creatinine, liver function tests or creatinine kinase were observed (**Table 3**). All patients were compliant with treatment with no significant difference between groups (data not shown). Only one patient (randomized to the A40 group) reported myalgias albeit without elevated creatine kinase (CK) levels.

4. Discussion

In the present study we compared the efficacy and safety of two different doses of atorvastatin (30 vs 40 mg/day) in high-risk patients. This is the first study that directly compared these doses of atorvastatin.

No significant differences were observed regarding the changes of LDL-C and other lipid parameters between the two groups. Regarding carbohydrate metabolism, A30 was associated with a numerically less increase of HOMA-IR and HbA1c in a random subgroup of non-diabetic subjects, which however was not significantly different compared with the A40 group. Both treatments were equally well tolerated.

Data from the VOYAGER (an indiVidual patient data meta-analysis Ofstatin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatinand simvastatin) meta-analysis database showed that the LDL-C reduction of atorvastatin 40 mg has a significant variation (47.9±13.8%) [12]. Our data show a slightly lower (44.1%) reduction of LDL-C with atorvastatin 40 mg after 3 months of treatment but still within the range of the expected decrease. Moreover, there is evidence that lower doses of atorvastatin (10-20 mg/day) have more advantageous effects on HDL-C and ApoAI compared with higher (40-80 mg/day) doses [13]. However, in our study no significant changes in serum HDL-C and ApoAI levels were observed in both groups.

A concern is the positive and dose-depended association between statin treatment and diabetes development [14]. A meta-analysis with 32,752 participants compared the risk of new diabetes between intensive and moderate dose statin therapy [15]. The intensive statin treatment was associated with higher incidence of new-onset diabetes compared with moderate treatment [odds ratio (OR) 1.12; 95% confidence interval (CI) 1.04-1.22] [15]. Moreover, a study comparing atorvastatin 20 and 40 mg/day showed that the higher dose led to a statistically significant deterioration of carbohydrate metabolism parameters compared with the lower dose [16]. In our study in a random sample of non-diabetic patients (n=50) a numerically lower increase in HOMA-IR index and HbA1c levels were observed in the A30 as compared with the A40 group. The lack of significance may be attributed to the small number of patients and the short follow-up period.

A major determinant of statin treatment efficacy on lipid lowering and consequently CVD prevention is compliance with treatment. Indeed, studies have associated poor statin adherence with an increased risk of CVD outcomes for both primary and secondary prevention [17]. Higher intensity statin therapy is associated with a modest but significantly lower compliance compared with low- or modest intensity statin therapy [18]. In our study, compliance in both groups was similar.

Among the various causes of poor compliance, adverse effects play a major role [19, 20]. Various studies have shown that the prevalence of statin-associated adverse effects is dose-depended [9]. Indeed, a meta-analysis showed that high-dose (atorvastatin or simvastatin 80 mg) vs moderate-dose (atorvastatin 10 mg, simvastatin 20 mg or pravastatin 40 mg) therapy was associated with a significant increase of any adverse event (OR = 1.44; 95% CI, 1.33-1.55; p< 0.001) and of adverse events requiring discontinuation of therapy (OR=1.28; 95%CI, 1.18-1.39; p<0.001) [21]. Moreover, high-dose statin therapy was associated with an increased risk for abnormalities of liver function tests (OR=4.48; 95% Cl, 3.27-6.16; p<0.001) and elevations in CK (OR=9.97; 95% CI, 1.28-77.92; p=0.028) [21]. In this study, A30 and A40 groups exhibited a similar safety profile.

5. Study limitations

This was an open-label study with a relatively small number of patients and a short treatment observation period. However, endpoints were blindly assessed.

6. Conclusion

Treatment with atorvastatin 30 mg/day is associated with the same efficacy in LDL-C lowering compared with atorvastatin 40 mg/day. Both regimens were equally well tolerated. A numerically lower increase in HOMA-IR and HbA1c was seen with A30 in a subgroup of non-diabetic subjects.

Conflict of interest

There is no conflict of interest.

Περίληψη

Πολυκεντρική μελέτη της αποτελεσματικότητας της ατορβαστατίνης 30 mg σε σύγκριση με ατορβαστατίνη 40 mg σε ασθενείς με πρωτοπαθή υπερχοληστερολαιμία

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Εισαγωγή: Για την επίτευξη των στόχων της υπολιπιδαιμικής αγωγής σε ασθενείς υψηλού κινδύνου απαιτείται η χορήγηση στατίνης υψηλής αποτελεσματικότητας, όπως η υψηλή δόση ατορβαστατίνης. Ωστόσο, η επιθετική υπολιπιδαιμική θεραπεία με στατίνες συσχετίζεται με αυξημένη επίπτωση ανεπιθύμητων ενεργειών, υψηλότερο οικονομικό κόστος, καθώς και με υψηλότερα ποσοστά διακοπής της θεραπείας. Στη χώρα μας πρόσφατα κυκλοφόρησε η μορφή της ατορβαστατίνης σε δισκία των 30 mg. Ωστόσο, δεν υπάρχουν δεδομένα για την αποτελεσματικότητα και την ασφάλεια αυτής της δοσολογίας στην κλινική πράξη.

Σκοπός: Η εκτίμηση της επίδρασης στο λιπιδαιμικό προφίλ και σε μεταβολικές παραμέτρους του ορού της χορήγησης ατορβαστατίνης 30 mg/ημέρα σε σύγκριση με τη χορήγηση ατορβαστατίνης 40 mg/ημέρα.

Μέθοδοι: Σε αυτή την πολυκεντρική μελέτη συμμετείχαν ασθενείς υψηλού κινδύνου, των οποίων τα επίπεδα της χοληστερόλης των χαμηλής πυκνότητας λιποπρωτεϊνών (LDL-C) ήταν εκτός στόχου. Οι ασθενείς τυχαιοποιήθηκαν σε ατορβαστατίνη 30 mg/ημέρα (A30) ή ατορβαστατίνη 40 mg/ημέρα (A40). Ο επανέλεγχός των ασθενών έγινε 3 μήνες μετά την έναρξη της θεραπευτικής παρέμβασης.

Αποτελέσματα: Οι ασθενείς (n=141; 75 άνδρες; μέση ηλικία 56 έτη) είχαν παρόμοιο λιπιδαιμικό προφίλ κατά την έναρξη της μελέτης (p=NS μεταξύ των ομάδων). Παρατηρήθηκαν παρόμοιες μεταβολές των λιπιδαιμικών παραμέτρων στις δύο ομάδες της μελέτης. Ειδικότερα, η LDL-C μειώθηκε κατά 42,1% στην ομάδα A30 έναντι 44,1% στην ομάδα A40 (p=NS). Δεν παρατηρήθηκαν σημαντικές μεταβολές των παραμέτρων της ομοιοστασίας των υδατανθράκων και στις δύο ομάδες. Η θεραπεία έγινε εξίσου καλά ανεκτή και στις δύο ομάδες.

Συμπεράσματα: Η χορήγηση της ατορβαστατίνης 30 mg/ημέρα είχε ως αποτέλεσμα παρόμοια μείωση της LDL-C σε σύγκριση με τη χορήγηση της ατορβαστατίνης 40 mg/ημέρα.

Λέξεις ευρετηρίου: Ατορβαστατίνη, λιπιδαιμικό προφίλ, μεταβολισμός υδατανθράκων, ανεπιθύμητες ενέργειες

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