Original Article

Long-term statin therapy could be efficacious in reducing the lipoprotein (a) levels in patients with coronary artery disease modified by some traditional risk factors

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Background: Lipoprotein (a) [Lp (a)] is a well-established risk factor for coronary artery disease (CAD). However, up till now, treatment of patients with higher Lp (a) levels is challenging. This current study aimed to investigate the therapeutic effects of short-, medium and long-term statin use on the Lp (a) reduction and its modifying factors.

Methods: The therapeutic duration was categorized into short-term (median, 39 days), medium term (median, 219 days) and long-term (median, 677 days). The lipid profiles before therapy served as baselines. Patients at short-, medium or long-term exactly matched with those at baseline. Every patient's lipid profiles during the follow-ups were compared to his own ones at baselines.

Results: The current study demonstrated that long-term statin therapy significantly decreased the Lp (a) levels in CAD patients while short-term or medium term statin therapy didn't. When grouped by statin use, only long-term simvastatin use significantly decreased the Lp (a) levels while long-term atorvastatin use insignificantly decreased the Lp (a) levels. Primary hypertension (PH), DM, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) could modify the therapeutic effects of statin use on the Lp (a) levels in CAD patients.

Conclusions: The long-term statin therapy could be efficacious in reducing the Lp (a) levels in CAD patients, which has been modified by some traditional risk factors. In the era of commercial unavailability of more reliable Lp (a) lowering drugs, our findings will bolster confidence in fighting higher Lp (a) abnormalities both for patients and for doctors.

Keywords: Lipoprotein (a) [Lp (a)]; statins; therapy; modifying factors

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Introduction

Lipoprotein (a) [Lp (a)] is a well-established risk factor for coronary artery disease (CAD) (1-4). However, up till now, treatment of patients with higher Lp (a) levels is challenging. Apheresis technique is potent and effective in reducing the Lp (a) levels, but is also expensive and cumbersome. The promising drugs, including mipomersen (5,6), lomitapide (7) and protein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (8,9) and antisense oligonucleotide (ASO) (10-12), are being intensively investigated, but are far from be widely used in clinical practice. Therefore, higher Lp (a) levels have often bogged down both doctors and patients. Statins are potent and effective low density lipoprotein cholesterol (LDL-C) lowering drugs that are widely used in clinical

practice to reduce the incidence of CAD, myocardial infarction, stroke, peripheral vascular disease, and improve the outcome of revascularization procedures (13). However, studies regarding statin therapeutic effects on reduction of Lp (a) levels are conflicting. Some studies showed confirmative therapeutic effects of statin on the Lp (a) reductions (14-16). A recent meta-analysis also found that atorvastatin modestly decreased the Lp (a) levels (17). However, other studies didn't find the statins' beneficial effects on the Lp (a) reductions (18-20). We think that it's reasonable the statins exhibit beneficial effects in reducing the Lp (a) levels given that the statins can deplete apolipoprotein B100 (apo B), which is indispensable to assemble the Lp (a). Furthermore, heterogeneities regarding patient enrollment, therapy duration and accompanied risk factors, which are neglected in the previous studies, may be the reasons causing the conflicting results. Therefore, it's necessary to investigate the therapeutic effects of stains on the Lp (a) reductions from different angles before we obtain access to more reliable Lp (a) lowering drugs. The current study aimed to investigate the therapeutic effects of short, medium and long-term statin use on the Lp (a) reduction and its modifying factors.

Methods

The database

Case Collection and Scientific reSearch System for Clinical Cardiology (CCSSSCC) database has been described elsewhere (21). Briefly, this is a desk top database file system. The database now includes around 40,000 consecutive patients admitted in the Division of Cardiology ever since Jan. 1st, 2002. The establishment of and the access to this database has been approved by the Institutional Review Boards of the 1st Affiliated Hospital and the Soochow University (No. 2016SZYYLL00598). All patient medical records were anonymized and de-identified. The institutional Review Board waived the need for informed consent before analysis as the nature of these data was retrospective. The current study conforms to the principles outlined in the Declaration of Helsinki.

Patient selection

Consecutive CAD patients, aged ≥16 years old, homogeneous in Chinese Han ethnicity, abstracted from the database, admitted from Jan. 1, 2010 through Dec. 31, 2013, were included for potential analysis. Exclusion criteria: (I) those with thyroid abnormalities; (II) those with liver function abnormalities; (III) those with kidney function abnormalities or uremia; (III) those with coexistence of any entities mentioned above; (V) those with no Lp (a) examinations; and (VI) those with statin switch. Only first diagnosed CAD patients, without prior statin use at baseline, but with repeat hospitalizations in the follow-ups, were enrolled for final analysis in the current study so that we could obtain the lipid profiles at different times, and that we could rule out the effects of previously possible statin use. Patients were admitted because of chief complaint of chest discomfort, with a confirmatory diagnosis of CAD by CAG at baseline, and were readmitted during follow-ups because of recurrent chest discomfort or reexamination of stented or diseased vessels.

Data on demographic factors, lifestyles, vital signs, comorbidities, blood glucose levels and lipid profiles were obtained. The data on height were missing in 3.44% of study subjects, fee in 0.34%, diastolic blood pressure (dbp) in 0.17%, and heart rate in 0.17% (*Table 1*).

Definitions, diagnoses and grouping

Definitions of smoking, drinking, and body mass index, and diagnosis of CAD, primary hypertension (PH), type 2 diabetes mellitus (T2DM), thyroid and kidney dysfunction have been described elsewhere in details (21). Briefly, chief complaints, cardiac biomarker exams, echocardiography, treadmill exercise test, Holter monitoring, separately or in combination, were used for diagnosing CAD. Notably, the coronary angiography was 100% performed for these study subjects.

We took advantage of patients' repeat hospitalizations to obtain the lipid profiles at different times. Short-term (median, 39 days) statin therapy was defined as greater than 7 days (inclusive) and less than 3 months (inclusive); medium term (median, 219 days), as greater than 3 months and less than 1 year (inclusive); and long-term (median, 677 days), as greater than 1 year. The statins and their dosages used in the current study are simvastatin with oral 40 mg once a day, atorvastatin with 20 mg, fluvastatin with 40 mg, and rosuvastatin with 10 mg. The lipid profiles before therapy served as baselines. At baseline, the first recordings were collected for a CAD patient with multiple lipid profile analyses. During follow-ups, the most recent recordings were collected for a patient with multiple lipid profile analyses in the same period of follow-up. Patients with Lipid profiles at short-term, medium term or long-term exactly matched with those at baseline. Every patient's lipid

Table 1 Baseline characteristics of CAD patients at first admission grouped by duration of follow-up

Characteristics	Missing values, n (%)	Baseline data at study entry	Baseline data matched with short-term	Baseline data matched with medium term	Baseline data matched with long-term	P values
N		582	165	250	270	
Demographic data						
Sex, n (male %)	0	462 (79.38)	130 (78.79)	202 (80.80)	210 (77.78)	0.6920
Age (yr)	0	–	67 (17.00)	67 (17.00)	68 (16.00)	0.8562
Insurance, n (%)	0	412 (71.03)	128 (77.58)	185 (74.60)	190 (70.63)	0.2450
Self-paid, n (%)	0	168 (28.97)	37 (22.42)	63 (25.40)	79 (29.37)	0.2450
Height (cm)	20 (3.44)	166 (10.00)	166 (10.00)	166 (9.00)	166 (10.00)	0.8662
Weight (kg)	0	65 (15.00)	64 (14.00)	66 (14.00)	65 (15.00)	0.0757
Marriage status, n (%)						
Divorced	0	1 (0.17)	1 (0.61)	0 (0)	0 (0)	0.2410
Married	0	572 (98.28)	161 (97.58)	248 (99.20)	263 (97.41)	0.2630
Unmarried	0	2 (0.34)	1 (0.61)	1 (0.40)	2 (0.74)	1.0000
Widowed	0	7 (1.20)	2 (1.21)	1 (0.40)	5 (1.85)	0.3520
Smoking, n (%)						
Never	0	262 (45.02)	64 (38.79)	118 (47.20)	132 (48.89)	0.1030
Current	0	220 (37.80)	73 (44.24)	86 (34.40)	91 (33.70)	0.0590
Past	0	100 (17.18)	28 (16.97	46 (18.40)	47 (17.41)	–
Alcohol consumption, n (%)						
Never	0	456 (78.35)	124 (75.15)	202 (80.80)	212 (78.52)	0.3940
Current	0	103 (17.70)	35 (21.21)	38 (15.20)	47 (17.41)	0.2940
Past	0	23 (3.95)	6 (3.64)	10 (4.00)	11 (4.07)	0.9720
Hospitalization information						
LOS (days)	0	9 (6)	11 (9)	9 (8)	9 (7)	0.0753
Outcome						
Death (%)	0	18 (3.09)	7 (4.24)	8 (3.20)	9 (3.33)	0.8420
Discharged live (%)	0	564 (96.91)	158 (95.76)	242 (96.80)	261 (96.67)	0.8420
Fee (¥)	2 (0.34)	36,050.82 (32,852.43)	36,771.83 (36,469.31)	35,228.75 (37,826.47)	35,918.75 (34,950.88)	0.8911
Sbp (mmHg)	0	130 (25.00)	126 (30.00)	130 (25.00)	130 (25.00)	0.0043
Dbp (mmHg)	1 (0.17)	78 (15.00)	74 (17.00)	80 (15.00)	80 (15.00)	0.0181
Heart rate (bpm)	1 (0.17)	73.5 (20.00)	75 (25.00)	73.5 (23.00)	73 (19.00)	0.1790

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Missing values, n (%)	Baseline data at study entry	Baseline data matched with short-term	Baseline data matched with medium term	Baseline data matched with long-term	P values
Medications						
Aspirin, n (%)	0	494 (84.88)	138 (83.64)	213 (85.20)	220 (81.48)	0.5210
ACEI/ARB, n (%)	0	403 (69.24)	111 (67.27)	172 (68.80)	188 (69.63)	0.8760
Beta blockers, n (%)	0	440 (75.60)	133 (80.61)	180 (72.00)	197 (72.96)	0.1020
CCB, n (%)	0	137 (23.54)	32 (19.39)	64 (25.60)	74 (27.41)	0.1510
Statins						
Simvastatin, n (%)	0	303 (52.06)	76 (46.06)	135 (54.00)	161 (59.63)	0.0220
Rosuvastatin, n (%)	0	33 (5.67)	12 (7.27)	18 (7.20)	7 (2.59)	0.0240
Fluvastatin, n (%)	0	6 (1.03)	2 (1.21)	2 (0.80)	4 (1.48)	0.8220
Atorvastatin, n (%)	0	240 (41.24)	75 (45.45)	95 (38.00)	98 (36.30)	0.1510
Nitrates, n (%)	0	242 (41.58)	73 (44.24)	96 (38.40)	115 (42.59)	0.4410
Clopidogrel, n (%)	0	473 (81.27)	135 (81.82)	197 (78.80)	204 (75.56)	0.2930
Type 2 diabetes, n (%)	0	169 (29.04)	50 (30.30)	71 (28.40)	79 (29.26)	0.9160
PH, n (%)	0	408 (70.10)	109 (66.06)	183 (73.20)	194 (71.85)	0.2740
Lipid profiles and sugar levels						
LDL-C (mmol/L)	0	2.58 (1.12)	2.57 (1.12)	2.51 (1.14)	2.60 (1.12)	0.5152
TC (mmol/L)	0	4.16 (1.49)	4.16 (1.60)	4.13 (1.45)	4.21 (1.40)	0.5265
TG (mmol/L)	0	1.24 (1.03)	1.23 (0.91)	1.25 (1.07)	1.25 (1.02)	0.9807
Lp (a) (mg/L)	0	105.85 (237.00)	104 (227.00)	105.85 (216.00)	109 (245.00)	0.6853
Sugar (mmol/L)	0	5.67 (2.06)	5.88 (2.15)	5.81 (2.08)	5.65 (2.11)	0.5765
Apo A (g/L)	0	1.21 (0.23)	1.20 (0.24)	1.22 (0.24)	1.21 (0.22)	0.8560
Apo B (g/L)	0	0.94 (0.36)	0.94 (0.43)	0.93 (0.34)	0.94 (0.36)	0.6222
Ratio of apo A to apo B	0	1.30 (0.5)	1.20 (0.70)	1.30 (0.30)	1.20 (0.50)	0.7356
HDL-C (mmol/L)	0	1.00 (0.27)	1.00 (0.27)	1.00 (0.27)	1.00 (0.28)	0.8259

Continuous variables were expressed as median (IQR), categorical ones, as frequencies and percentages. P values indicate comparisons among baseline values of short-term, medium term and long-term groups. The number of overall patients doesn't equal the summation of 165, 250 and 270 in the three groups as a patient with lipid profiles at baseline may not undergo lipid profile analysis at short-term, medium term or long-term. Therefore, always a part of patients during follow-ups of short-term, medium term or long-term can find the exact matches at baseline. CAD, coronary artery disease; LOS, length of hospital stay; sbp, systolic blood pressure; dbp, diastolic blood pressure; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; PH, primary hypertension; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; apo A, apolipoprotein A; apo B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol.

profiles during the follow-ups were compared to his own ones at baselines. Thus, we made up the three before-after treatment groups.

Lp (a) measurement

The Lp (a) measurement method has been described in details elsewhere. Briefly, determination of the Lp (a) levels was performed using the latex-enhanced immunoturbidimetric diagnostic reagent kits. The assay range is 10–1,000 mg/L. The blood samples with Lp (a) levels >1,000 mg/L were routinely diluted 1:10. Thus, the Lp (a) concentrations up to 10,000 mg/L were within the security range of the assay and wouldn't mistakenly be considered as a low level due to antigen excess. Lp (a) protein calibrator, in accordance with the IFCC PRM-2, provided by Sekisui Co. Ltd., has been used to calibrate the Lp (a) diagnostic reagents. The intra-assay and inter-assay coefficients of variation for Lp (a) were 2.5% and 3.11%, respectively.

Follow-ups

Repeat hospitalized patients with multiple lipid profile analyses were specifically focused as these patients made up an ideal population for a before-after study. CAD patient follow-ups after discharge were conducted in CAD clinics on a monthly basis for the first 4 months and on a bimestrial basis for the remaining 8 months, so as to know about patients' symptoms, signs, drug administration and relevant imaging or lab examination results. For those who failed to visit the clinics, we called those patients or their relatives to know about the above-mentioned information. Particular attention has been paid to patients' compliances with statin use. All information was written down in a standardized spreadsheet for future analysis.

Statistical analysis

Shapiro-Wilk test was hired for examining the characteristics of distribution of continuous variables. Continuous variables conforming to normal distribution were expressed as MEAN ± SD, otherwise, as median (interquartile range, IQR). Categorical variables were expressed as frequencies and percentages. Likelihood ratio chi squared test was used for comparison of frequencies or percentages among different groups. Kruskal-Wallis rank test was used for multiple independent sample comparisons as the variables were not distributed normally. Multilevel mixed effects model was used to compare changes of lipid profiles before and after-treatment. Patients were dichotomously divided according to presence or absence of some baseline characteristics, or arbitrarily divided into thirds in terms of LDL-C and HDL-C levels at baseline so as to further examine the effects of statin on Lp (a) levels in different stratifications.

Results

There were a total of 5,082 person-time CAD patients, among whom, 510 were excluded because of failure to examine Lp (a); 3,003, because of single Lp (a) exam; 101, because of thyroid dysfunction, kidney dysfunction and coexistence of any entities above; 19, because of single Lp (a) exam result left again due to exclusion of patients with above-mentioned morbidities; 27, because of failure to follow up or of undergoing any statin dosage adjustment during the follow-up; and 15, because of statin use duration <7 days. Thus, a total of 1,369 person-time CAD patients met for final analysis, from whom, we made up the three self-control groups: 165 pairs with short-term therapy; 250 pairs with medium term therapy; and 270 pairs with long-term therapy. Details were seen in flow diagram (*Figure 1*).

Baseline characteristics of CAD patients at initial admission grouped by duration of follow-up

The baseline characteristics of CAD patients were largely well-balanced among the three therapeutic groups. More patients received simvastatin treatment in medium or long-term group as compared with those (54%, 59% *vs.* 46%) in short-term one. In contrast, more patients received rosuvastatin treatment in short or medium term group as compared with those (7%, 7% *vs.* 2%) in long-term one. Use of fluvastatin or atorvastatin was similar (Ps>0.05) among different groups (*Table 1*).

Lipid profile [other than Lp (a)] changes after short, medium or long-term therapy vs. baseline values, grouped by statin use

The concentrations in LDL-C, TC, HDL-C and apo B were consistently and significantly decreased (Ps<0.05) after short, medium or long-term statin therapy as compared with baseline levels. The concentrations of ratio of apo A to apo B were consistently and significantly increased (Ps<0.05) after short, medium or long-term statin therapy as compared with baseline levels. The concentrations of

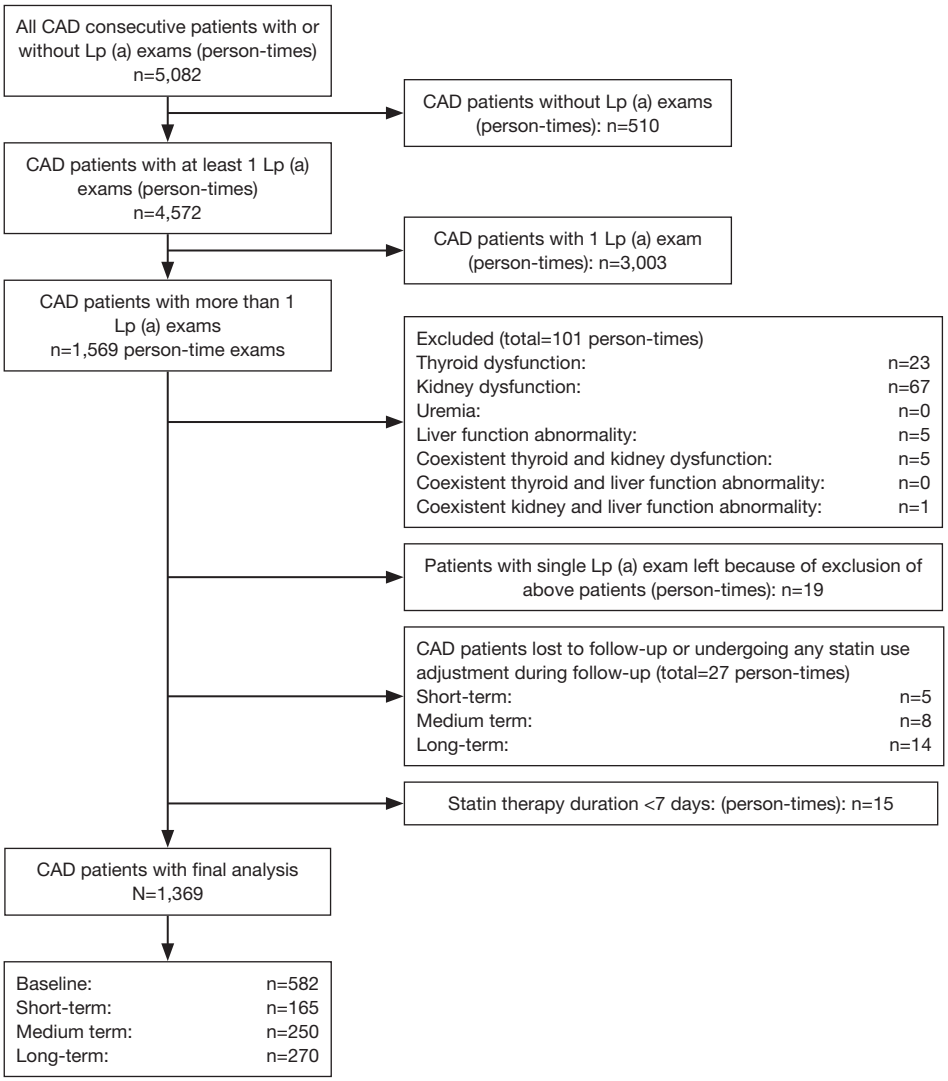

Figure 1 Flow chart of patient selection. The number of patients entered for final analysis is 1,369, not equaling the summation of 582+165+250+270. See the explanations presented in notes in *Table 1*.

TG were significantly decreased (Ps<0.05) after short- or medium term statin therapy as compared with those baseline levels. However, the therapeutic effects of statin on TG disappeared over a long-term statin use. The statin use had no any effects on apo A (*Table 2*).

Lp (a) changes after short, medium or long-term therapy vs. baseline values, grouped by statin use

Overall, a trend towards lowering Lp (a) concentrations was consistently demonstrated after short-term, medium term or long-term statin therapy as compared with baseline levels. However, only after long-term statin therapy, did the trend reach the significant level (P=0.0011). When grouped by statin use, only long-term simvastatin therapy significantly decreased the Lp (a) levels as compared with baseline values. Atorvastatin, fluvastatin or rosuvastatin showed therapeutic effects on Lp (a), but without statistical significances (*Table 3*).

Lp (a) changes after short-, medium or long-term therapy vs0 baseline values, stratified by PH, DM, LDL-C and se.

Stratification analysis revealed that the Lp (a) levels were overall decreased in whatever follow-up durations in whatever stratifications. Interestingly, only in long-term statin use in

Table 2 Lipid profile [other than Lp (a)] changes after short-, medium or long-term statin therapy *vs.* baseline

Characteristics	Baseline	Short-term	P values	Baseline	Medium term	P values	Baseline	Long-term	P values
Median time (days)	–	39	–	–	219	–	–	677	–
N	165	165		250	250		270	270	
LDL-C (mmol/L)	2.57 (1.12)	1.88 (0.94)	<0.0001	2.51 (1.14)	2.00 (0.85)	<0.0001	2.60 (1.12)	2.07 (0.90)	<0.0001
TC (mmol/L)	4.16 (1.60)	3.22 (1.27)	<0.0001	4.13 (1.45)	3.23 (1.18)	<0.0001	4.21 (1.40)	3.31 (1.03)	<0.0001
TG (mmol/L)	1.23 (0.91)	1.12 (0.82)	0.0046	1.25 (1.07)	1.10 (0.78)	0.0003	1.25 (1.02)	1.14 (0.99)	0.2086
Apo A (g/L)	1.20 (0.24)	1.17 (0.21)	0.1632	1.22 (0.24)	1.19 (0.23)	0.0508	1.21 (0.22)	1.20 (0.24)	0.3285
Apo B (g/L)	0.94 (0.43)	0.76 (0.34)	<0.0001	0.93 (0.34)	0.76 (0.34)	<0.0001	0.94 (0.36)	0.77 (0.29)	<0.0001
Ratio of apo A to apo B	1.20 (0.70)	1.50 (0.80)	<0.0001	1.30 (0.30)	1.60 (0.60)	<0.0001	1.20 (0.50)	1.60 (0.50)	<0.0001
HDL-C (mmol/L)	1.00 (0.27)	0.96 (0.27)	0.0298	1.00 (0.27)	0.98 (0.21)	0.0052	1.00 (0.28)	0.96 (0.24)	0.0140

Continuous variables were expressed as median (IQR). P values indicate comparisons between short-, medium or long-term and baseline using multilevel mixed model. LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; apo A, apolipoprotein A; apo B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol.

some stratifications, were there significantly reduced Lp (a) levels as compared with baseline. The exception is in the mid tertile of LDL-C (2.18–3.03 mmol/L), where statin use increased the Lp (a) levels by ~10% across all durations of follow-up. Short-term and medium term statin therapy didn't show any significant changes in Lp (a) levels in any stratifications (*Table 4*).

Discussions

The current study has demonstrated that long-term statin therapy significantly decreased the Lp (a) levels in CAD patients while short-term or medium term statin therapy didn't. When grouped by statin use, only long-term simvastatin use significantly decreased the Lp (a) levels. PH, DM, LDL-C and HDL-C could modify the therapeutic effects of statin use on the Lp (a) levels in CAD patients.

As expected, the LDL-C, TC and apo B levels were markedly, consistently and significantly decreased after short-term, medium term or long-term statin therapy as compared with baselines, which were consistent with previous reports (22-24).

The findings in the current study that the short or medium term statin therapy didn't reduce the Lp (a) levels have been lent support by several studies. Treatment with 20, 40, and 80 mg atorvastatin even for 24 weeks unexpectedly increased the Lp (a) levels by 9%, 8%, and 10% in CAD patients (19). MIRACL study also showed 16 weeks of treatment with 80 mg atorvastatin resulted in a significant increase of Lp (a) in acute coronary syndrome patients (20). A large, randomized, double blind and multicenter trial showed that simvastatin treatment for 24 weeks was not associated with a change in Lp (a) concentrations relative to placebo in primary hypercholesterolemia patients with LDL-C >190 mg/dL (18). In contrast, long-term statin therapy exhibited a significant reduction of Lp (a) level in several other studies, which was consistent with our findings. A 2-year, randomized, double blind trial revealed that treatment with 80 mg atorvastatin or 40 mg simvastatin significantly decreased the Lp (a) levels in familial hypercholesterolemia after 1 year and after 2 years (all P<0.0001), respectively. Atorvastatin therapy was more efficacious in reduction of Lp (a) levels (P=004) as compared with simvastatin at 1 year, but wasn't any more (P=0.086) at 2 years (16). Another prospective, placebo-controlled randomized trial revealed that the Lp (a) levels were significantly decreased after 36 weeks atorvastatin therapy in dialysis patients (15). Our study also showed that only simvastatin exhibited beneficial effects of reduction of Lp (a) levels, which were different from prior studies (14-16). But we didn't think simvastatin was different from atorvastatin in reduction of Lp (a) levels as the sample size in the current study was smaller in atorvastatin treatment group than in simvastatin one (98 *vs.* 161) with no sufficient statistical power to negate atorvastatin's beneficial effects on Lp (a) reduction.

Statins inhibit cholesterol synthesis and activate LDL receptor, thus decreasing the levels in LDL-C and apo B, among which, apo B is a vehicle and a ligand for transporting and degrading endogenous cholesterol synthesized in liver

Table 3 Short-term, medium term and long-term therapeutic effects on Lp (a) levels *vs.* baseline values, grouped by statin use

Statin use	Dosage (mg/day)	N	Baseline	Short-term	P values	N	Baseline	Medium term	P values	N	Baseline	Long-term	P values
Median time (days)	–		–	39	–		–	219	–		–	677	–
Simvastatin	40	76	94.5 (178.0)	90 (232.65)	0.7202	135	105 (190.7)	104 (229.6)	0.3971	161	105 (181.0)	80 (167.0)	0.0109
Rosuvastatin	10	12	100 (122.5)	115 (148.00)	0.5000	18	192.5 (416.0)	114.5 (355.0)	0.0963	7	58 (72.0)	21 (76.0)	1.0000
Fluvastatin	40	2	106.5 (17.0)	223.5 (205.00)	0.5000	2	106.5 (17.0)	75 (10.0)	1.0000	4	144.2 (229.3)	88.5 (161.0)	0.6250
Atorvastatin	20	75	105 (287.0)	95 (286.00)	0.8099	95	105 (220.0)	90 (202.0)	1.0000	98	128.5 (297.0)	124.5 (372.0)	0.0822
Overall	–	165	104 (227.0)	95 (247.00)	0.4655	250	105.85 (216.0)	96.5 (228.6)	0.7027	270	109 (245.0)	90.5 (225.0)	0.0011

The Lp (a) levels were expressed as median (IQR). P values indicate comparisons between short-, medium or long-term and baseline using multilevel mixed model.

Table 4 Short-term, medium term and long-term therapeutic effects on Lp (a) levels *vs.* baseline values, stratified by PH, DM, sex, LDL-C and HDL-C

Characteristics	Lp (a) levels				Lp (a) levels				Lp (a) levels			
	N	Baseline	Short-term	P values	N	Baseline	Medium term	P values	N	Baseline	Long-term	P values
Median time (days)		–	39	–		–	217	–		–	677	–
PH												
Yes	109	105 (227.0)	95 (231.0)	1.0000	183	105.7 (219.00)	94 (233.0)	0.6040	194	103.55 (189.2)	81.5 (174.0)	0.0037
No	56	97 (232.5)	93 (333.0)	0.2026	67	107 (216.00)	108 (216.0)	1.0000	76	118.40 (292.0)	128 (312.0)	0.1654
DM												
Yes	50	76.5 (170.0)	71.3 (153.0)	1.0000	71	94 (195.00)	72 (188.0)	0.9050	79	103 (189.0)	83 (216.0)	0.2127
No	115	115 (245.0)	106.8 (281.0)	0.4394	179	110 (234.00)	103 (238.0)	0.7638	191	109.7 (253.0)	91 (250.0)	0.0027
Sex												
Male	130	94.5 (214.0)	91.5 (206.0)	0.7140	202	105 (168.00)	91 (191.0)	0.3210	210	106 (236.0)	89.5 (223.0)	0.0305
Female	35	144 (357.0)	118 (323.0)	0.4869	48	158.5 (390.75)	130.5 (400.5)	0.3123	60	128.5 (254.0)	94.5 (254.0)	0.0062
LDL-C (mmol/L)												
≤2.18	55	78 (130.0)	90 (147.0)	0.5831	91	65 (153.00)	69 (133.0)	1.0000	84	102 (165.0)	72 (155.5)	0.1873
2.18–3.03	55	90 (343.0)	89 (266.0)	0.8877	81	115.8 (261.00)	135 (250.0)	0.9111	96	80.5 (182.0)	88 (163.5)	0.0134
>3.03	55	147.9 (297.0)	116 (371.8)	0.7754	78	144 (325.00)	115 (249.0)	0.6488	90	168.5 (389.0)	142.5 (362.0)	0.1093
HDL-C (mmol/L)												
≤0.93	56	99.5 (313.0)	102 (305.0)	0.4885	90	110.6 (208.00)	98.5 (229.0)	0.9152	93	98 (193.0)	78 (142.0)	0.0470
0.93–1.11	54	96 (180.0)	69 (165.0)	0.3916	81	105 (267.50)	95 (260.0)	0.1193	86	124.4 (266.8)	114 (361.0)	0.1284
>1.11	55	110.6 (195.2)	106 (222.0)	0.1608	79	100 (195.00)	83 (225.0)	0.3082	91	109 (263.0)	95 (253.0)	0.0558
Overall	165	104 (227.0)	95 (247.0)	0.4655	250	105.85 (216.00)	96.5 (228.6)	0.7027	270	109 (245.0)	90.5 (225.0)	0.0011

The Lp (a) levels were expressed as median (IQR). P values indicate comparisons between short-, medium or long-term and baseline using multilevel mixed model. PH, primary hypertension; DM, type 2 diabetes mellitus; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

(25,26). Apo B is also an indispensable component for assembling the Lp (a), which includes apolipoprotein (a) and LDL-C particle bound covalently by a disulfide between apolipoprotein (a) and apo B of LDL (27). The residence time of Lp (a) is longer than that of apo B in plasma (28). The inhibitory effects of statin on cholesterol synthesis are more pronounced than on apo B, or it takes more time to decrease the apo B levels, resulting in Lp (a) reductions, which may in part explain the findings revealed in the current study that only the long-term statin use is able to decrease the Lp (a) levels. We have to admit that the precise mechanism of the long-term statin use on Lp (a) reductions remains to be elucidated.

The current study revealed that risk factors, such as PH, DM, LDL-C and HDL-C, could modified the effects of statin use on Lp (a) reductions in patients with CAD. That higher Lp (a) levels in hypertensive patients were found than in normal controls seemed to support our findings in the stratification analysis that statin therapy could decrease the Lp (a) levels in hypertensive patients, but couldn't in the normotensive patients (29). The higher Lp (a) levels would be more easily blunted by drug intervention. This explanation has been further supported by the findings revealed in the current study that only non DM patients' Lp (a) levels were significantly decreased by statin treatment. Several studies showed that the Lp (a) levels were inversely associated with incident DM, which we think also partly explained the stratifying effects by DM in the current study (30-32).

Unexpectedly, in the mid tertile of LDL-C levels, the statin therapy almost consistently increased the Lp (a) levels across the short, medium and long-term groups, and reached the significant levels (P=0.0134) in the increase of the Lp (a) levels after long-term therapy. In contrast, the statin therapy insignificantly decreased the Lp (a) levels in the bottom or the top tertile of LDL-C levels across the short, medium and long-term groups. Similarly, in normotensive patients, the short or medium statin therapy was almost unchanged in the Lp (a) level reductions as compared with baselines. In contrast, the long-term statin therapy increased the Lp (a) levels although it didn't reach the significant levels (118.4 *vs.* 128, P=0.1654). We cannot explain these phenomena, but they remind us it may be important to treat those high Lp (a) level patients with statins based on patients' different risk factors (33).

Limitations

Our study has several limitations: first, observational study is susceptible to confounding factors, which may attenuate or exaggerate the observed effects of statin use on Lp (a) levels. Strictly matched pair wise analysis minimized these influences. Second, the current study selected the patients with multiple hospitalizations, and the majority of patients in the current study did not have repeat Lp (a) measured thus, the selection bias is potential and the generalization of our results should be cautious. Finally, we did not stratify the patients according to the severity of diseased coronary vessels although all the patients in the current study underwent coronary angiography exam. The severity of diseased vessels will affect patients' hospitalizations and therapeutic effects. Further study is warranted to confirm our findings.

In conclusion, the long-term statin therapy is efficacious in reducing the Lp (a) levels in CAD patients, which has been modified by some traditional risk factors. Administration of statins with sufficient time as well as appropriate selection of CAD patients according to risk factors may be important so as to obtain the beneficiary effects of the Lp (a) reductions in CAD patients. We think the statin use duration > 1 year is appropriate based on the current study and previous reports (15, 16). In the era of commercial unavailability of more reliable Lp (a) lowering drugs, our findings will bolster confidence in fighting higher Lp (a) abnormalities for both patients and doctors. Large sample sized studies, specifically focusing on therapeutic effects of long-term statin use on the Lp (a) levels, were warranted to confirm our findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The establishment of and the access to this database has been approved by the Institutional Review Boards of the 1st Affiliated Hospital and the Soochow University (No. 2016SZYYLL00598). The institutional Review Board waived the need for informed consent before analysis as the nature of these data was retrospective.

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