Clinical and Applied Thrombosis/Hemostasis
Volume 26: 1-7
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1076029620920369
journals.sagepub.com/home/cat
SAGE

Changes in Homocysteine Levels Affect Serum Lipid Response to Atorvastatin in Patients With Acute Coronary Syndrome: A Retrospective Observational Study

Dong-Feng Wu, MD[1], Yin-Xiong Wu, MSc[1], and Jin-Long Deng, MSc[1]

Abstract

Objective: The present study investigated whether changes in serum homocysteine (Hcy) levels modify the effects of atorvastatin treatment on blood lipid parameters in patients with acute coronary syndrome (ACS). **Methods:** A total of 159 patients with ACS who received regular, long-term treatment with 20 mg/d atorvastatin were included. Depending on the changes in Hcy parameters, they were divided into Hcy reduction (HR) and Hcy elevation (HE) groups. **Results:** After long-term atorvastatin treatment, total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, and Hcy levels were decreased ($P < .05$), and the ApoAI level was increased ($P < .01$). Correlation and stratified analysis showed that Hcy or hyperhomocysteinemia was correlated with blood lipids. In both the HE and HR groups, the TC, LDL-C, and ApoB levels after treatment were lower than those before treatment ($P < .01$), and the ApoAI level was increased compared with that before treatment ($P < .05$). There was no difference in the reduction of TC, LDL-C, and ApoB levels or in the increase of ApoAI level ($P_{interaction} > .05$) between the 2 groups. However, there was a clear opposite trend of the effect of atorvastatin on TG and high-density lipoprotein cholesterol (HDL-C) levels between the HR and HE groups ($P_{interaction} < .05$). In the HR group, the HDL-C level was increased ($P < .05$), and TGs were decreased compared with those before treatment ($P < .01$). Nevertheless, in the HE group, the HDL-C level was decreased ($P < .05$), and TGs ($P < .05$) were increased compared with those before treatment. **Conclusion:** The effects of atorvastatin on TGs and HDL-C depend on changes in Hcy levels. Patients with a reduced Hcy level after atorvastatin treatment had more favorable lipid parameters.

Keywords

acute coronary syndrome, atorvastatin, lipid, homocysteine

Date received: 4 January 2020; revised: 17 March 2020; accepted: 24 March 2020.

Introduction

The prevalence and death rate of cardiovascular disease in China are still on the rise according to the "Report on Cardiovascular Diseases in China 2018." Notably, acute coronary syndrome (ACS) accounts for 50% of cardiovascular deaths and is the most common and high-risk type of coronary heart disease (CHD), including unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction. Despite the development of percutaneous coronary intervention (PCI) technology, patients still have a high incidence of major adverse cardiovascular events after ACS. The CHD mortality rate of urban and rural residents in China has gradually been increasing since 2012.[1] Therefore, drug therapy for secondary prevention of CHD is one of the key treatment measures used to reduce the incidence of ACS regardless of PCI therapy. Atorvastatin is a lipid-lowering agent from β-hydroxy β-methyl glutaryl-CoA inhibitors. At the standard dosage, this drug reduces total cholesterol (TC) levels by 20% to 30%, low-density lipoprotein cholesterol (LDL-C) levels by 21% to 60%, and triglyceride (TG) levels by 7% to 37% and increases high-density lipoprotein cholesterol (HDL-C) levels by approximately 5% to 10%.[2] At present,

[1] Department of the Geriatric Cardiology, People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China

Corresponding Author:
Jin-Long Deng, Department of Geriatric Cardiology, People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Nanning 530021, Guangxi, People's Republic of China.
Email: djl_gx@163.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

Table 1. Clinical Information of Selected Patients.

Factor	Parameter
Age, year	62.36 ± 10.94
Gender, male/female	108/51
BMI, kg/m^2	23.42 ± 3.68
Hypertension	63
Diabetes	12
Time after PCI (month)	9.34 ± 3.65
Clinical type	
ST-segment elevation myocardial infarction	58
Non-ST-segment elevation myocardial infarction	42
Unstable angina	59

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention.

China's guidelines recommend atorvastatin for patients with very high-risk stratification, such as patients with ACS, and the primary target value of LDL-C after statin therapy should be below 1.8 mmol/L; if the LDL-C at baseline is within the target value, the LDL-C should be further reduced by approximately 30%. If the LDL-C baseline value is high and reducing the LDL-C to the primary target value is difficult, the guideline recommends decreasing the LDL-C by at least 50% as an alternative target.[3]

Recent epidemiological studies have found that serum homocysteine (Hcy) is a new risk factor for cardiovascular diseases such as CHD.[4,5] Moreover, clinical studies have shown that statin therapy can reduce human Hcy levels.[6] It was also found that Hcy levels were associated with decreased HDL-C and ApoAI levels and increased TC and LDL-C levels.[7] However, it is unclear whether there is an interaction between the reduction in Hcy level and the effect of lipid-lowering therapy after atorvastatin treatment. To the best of our knowledge, no report has addressed this question in the literature. Therefore, this study investigated the changes in serum Hcy and lipid levels in patients with ACS treated with long-term statin therapy after undergoing PCI and further explored whether the changes in Hcy levels after statin treatment affect the lipid-lowering effect of the drug.

Materials and Methods

Patients

A total of 159 patients (108 males and 51 females) who were diagnosed with ACS and treated with PCI in the geriatric cardiovascular ward of Guangxi Zhuang Autonomous Region People's Hospital were enrolled in this study from January 2016 to January 2018 (see Table 1 for clinical information). The enrolled patients received long-term treatment with 20 mg/d atorvastatin (at least 1 year; to some extent, the course of treatment is lifelong, unless the level of LDL-C falls below 1.8 mmol/L) after being diagnosed with ACS. The following patients were excluded: (1) patients with severe liver and kidney function damage; (2) patients with endocrine and metabolic diseases; (3) patients with systemic diseases such as autoimmune diseases; (4) patients taking folic acid, vitamin B12, and other lipid-lowering drugs; (5) patients with other known causes of heart disease; and (6) patients who did not complete follow-up. All patients signed informed consent when they were admitted to the hospital. The study was approved by the Ethics Committee of Guangxi Zhuang Autonomous Region People's Hospital.

Data Collection and Laboratory Methods

Medical history data, including diabetes, hypertension, and other cardiovascular diseases, were collected for all selected patients. The physical examination including blood pressure, height, weight and abdominal circumference, and body mass index (BMI) was calculated according to height and weight. On the second day after admission, antecubital venous blood from the forearm was taken on an empty stomach and sent to the Clinical Laboratory Center of Guangxi People's Hospital to detect blood lipids, Hcy, and other biochemical indicators. All of these indicators were measured by a Beckman Coulter AU 5831 automatic biochemical analyzer (Beckman Coulter Inc, Brea, California). TC, TG, HDL-C, and LDL-C levels in the samples were determined by enzymatic methods with commercially available kits. Serum ApoAI and ApoB levels were detected by immunoturbidimetric immunoassay. The level of serum Hcy was determined by the cyclic enzymatic method. All these measurements were performed in a single laboratory using the same assay conditions; moreover, the laboratory staff was blinded to all information about the enrolled patients. Hyperhomocysteinemia (HHcy) was defined as Hcy greater than 15 μmol/L.

Drug Information

All selected patients were routinely given 20 mg tablets of atorvastatin (Lipitor, Pfizer Pharmaceutical Factory, New York, USA) every night after admission. Emergency patients were given 600 mg of clopidogrel or 180 mg of ticagrelor and 300 mg of aspirin before the operation. All patients received 2 types of antiplatelet drugs (clopidogrel 75 mg/d or ticagrelor 90 mg twice daily [bid] plus aspirin 100 mg/d) 3 days before the operation. Before the operation, a clopidogrel 300-mg loading dose was given routinely. For those who did not receive antiplatelet therapy for 3 days before elective surgery, 300 mg of clopidogrel and 300 mg of aspirin were given routinely before the operation. All patients continued to receive long-term dual antiplatelet therapy (75 mg/d clopidogrel or 90 mg bid ticagrelor plus 100 mg/d aspirin) routinely after the operation, and they were treated with atorvastatin 20 mg/night for an extended period of time after the operation.

Research Groups

The study group was divided into 2 groups according to the changes in Hcy levels after atorvastatin treatment. If the

Table 2. Changes in Serum Lipids and Homocysteine Levels After Atorvastatin Treatment.[a]

Parameter	Pretreatment	Posttreatment	Discrepancy	*F*	*P*
TC, mmol/L	4.81 ± 1.09	3.91 ± 0.81	−0.91 ± 1.13	101.243	.000
TGs, mmol/L	1.82 ± 1.49	1.46 ± 0.73	−0.36 ± 1.45	9.834	.002
HDL-C, mmol/L	1.08 ± 0.28	1.09 ± 0.26	0.006 ± 0.24	0.105	.746
LDL-C, mmol/L	3.02 ± 0.78	2.24 ± 0.62	−0.78 ± 0.86	132.254	.000
ApoAI, g/L	1.13 ± 0.23	1.20 ± 0.20	0.07 ± 0.22	16.430	.000
ApoB, g/L	0.98 ± 0.23	0.76 ± 0.19	−0.21 ± 0.23	129.972	.000
Hcy, μmol/L	14.31 ± 5.96	13.41 ± 5.04	−0.90 ± 4.25	7.099	.009

Abbreviations: Apo, apolipoprotein; Hcy, homocysteine; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.
[a]N = 159.

patients' Hcy levels after treatment were higher than those before treatment, they were classified into the Hcy elevation (HE) group; if the patients' Hcy levels after treatment were lower than those before treatment, they were classified into the Hcy reduction (HR) group. The differences in blood lipid levels before and after atorvastatin treatment were compared between the 2 groups.

Statistical Analyses

SPSS 22.0 statistical software was used for statistical analysis of the research data. Quantitative variables were expressed as the mean ± standard deviation, and qualitative variables were expressed as counts. Correlations between Hcy and blood lipid parameters were determined using Pearson correlation analysis. Analysis of covariance was used to test the association of HHcy and serum lipid parameters. Repeated measures analysis of variance was used to analyze the changes in blood lipid parameters and Hcy levels before and after treatment, and $P < .05$ was considered indicative of statistical significance.

Results

Changes in Blood Lipid Levels and Hcy Levels After Atorvastatin Treatment

The blood lipid levels of TC, TGs, LDL-C, and ApoB were significantly decreased after atorvastatin treatment ($P < .005$). The ApoAI level was increased compared with the level before treatment ($P < .005$). However, there was no statistically significant difference in HDL-C levels ($P > .05$). After atorvastatin treatment, the serum Hcy level was significantly decreased compared with the level before treatment ($P < .05$), as shown in Table 2.

Correlation Between Hcy Levels and Blood Lipid Levels

Before atorvastatin treatment, Hcy levels were negatively correlated with HDL-C levels ($t = -0.192$, $P = .015$), while there was no significant correlation between levels of Hcy and TC, TGs, LDL-C, ApoAI, or ApoB, as shown in Table 3.

Table 3. Correlation Between Serum Lipids and Homocysteine Levels Before Treatment With Atorvastatin.[a]

Relative Factor	*t*	*P*
TC, mmol/L	−0.049	.540
TGs, mmol/L	0.121	.130
HDL-C, mmol/L	−0.192	.015
LDL-C, mmol/L	−0.040	.613
ApoAI, g/L	−0.058	.465
ApoB, g/L	−0.003	.973

Abbreviations: ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
[a]N = 159.

Hyperhomocysteinemia and Serum Lipid Levels

After adjustment for sex, age, and BMI, a statistical analysis performed between the normal Hcy and HHcy groups divided according to whether the serum Hcy concentration was greater than 15 μmol/L indicated that the levels of serum TGs in the HHcy group were significantly higher than those in the normal Hcy group and that the levels of serum HDL-C and ApoAI in the HHcy group were significantly lower than those in the normal Hcy group (P for all <.05; Table 4).

The Interaction Between the Change in Hcy Level and the Lipid-Lowering Effect

The patients were divided into HE group or HR group according to the change in Hcy level after treatment with atorvastatin, and the effect of atorvastatin on lipid regulation was compared between the 2 groups. In the HE and HR groups, the levels of TC, LDL-C, and ApoB significantly decreased, and the ApoAI level significantly increased after treatment compared with the levels before treatment ($P < .01$). There were no significant differences in the effects of lowering TC, LDL-C, and ApoB and increasing ApoAI between the 2 groups ($P_{\text{interaction}} > .05$). In the HE group, the TG levels after treatment were significantly higher than those before treatment ($P < .05$), while in the HR group, the TG levels after treatment were significantly lower than those before treatment ($P < .01$); the effects of atorvastatin on TG levels in the 2 groups were noticeably in

Table 4. Hyperhomocysteinemia and Serum Lipid Levels in Patients With ACS.

Group	N	TC, mmol/L	TGs, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	ApoAI, g/L	ApoB, g/L
Normal Hcy	99	4.81 ± 1.04	1.49 ± 1.06	1.15 ± 0.28	3.02 ± 0.80	1.16 ± 0.22	0.98 ± 0.23
HHcy	60	4.82 ± 1.17	2.37 ± 2.03	0.98 ± 0.21	3.03 ± 0.76	1.06 ± 0.23	0.98 ± 0.22
F		0.002	11.315	14.338	0.003	6.764	0.035
P		.964	.001	.000	.955	.010	.852

Abbreviations: ACS, acute coronary syndrome; ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; HHcy, hyperhomocysteinemia; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

Table 5. Comparison of Blood Lipid Levels Before and After Statin Treatment in the Different Hcy Groups.

	N	TC, mmol/L	TGs, mmol/L	HDL-C, mmol/L	LDL-C, mmol/L	ApoAI, g/L	ApoB, g/L
HE (n = 63)	Pretreatment	4.66 ± 1.09	1.19 ± 0.50	1.10 ± 0.33	2.95 ± 0.74	1.10 ± 0.28	0.96 ± 0.21
	Posttreatment	3.64 ± 0.74[a]	1.59 ± 0.90[b]	1.04 ± 0.30[b]	2.02 ± 0.46[a]	1.21 ± 0.23[b]	0.72 ± 0.19[a]
	Discrepancy	−1.02 ± 0.89	0.40 ± 0.71	−0.06 ± 0.28	−0.93 ± 0.64	0.11 ± 0.27	−0.24 ± 0.21
HR (n = 96)	Pretreatment	4.92 ± 1.10	2.10 ± 1.83	1.08 ± 0.22	3.07 ± 0.81	1.15 ± 0.19	0.99 ± 0.24
	Posttreatment	4.08 ± 0.82[a]	1.37 ± 0.58[a]	1.12 ± 0.22[b]	2.39 ± 0.67[a]	1.19 ± 0.19[b]	0.80 ± 0.19[a]
	Discrepancy	−0.83 ± 1.26	−0.73 ± 1.68	0.06 ± 0.20	−0.69 ± 0.97	0.05 ± 0.18	−0.19 ± 0.25
$P_{interaction}$	-	.309	.000	.008	.078	.095	.237

Abbreviations: ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; Hcy, homocysteine; HE, Hcy elevation, HR, Hcy reduction; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.
[a] Compared with before treatment, $P < .001$.
[b] Compared with before treatment, $P < .05$.

contrast ($P_{interaction} < .05$). In the HE group, the HDL-C levels after treatment showed a decreasing trend compared with the levels before treatment ($P < .05$). In the HR group, the HDL-C levels after treatment were significantly increased compared with the levels before treatment ($P < .05$). The effects of atorvastatin on HDL-C levels between the 2 groups were significantly opposite one another ($P_{interaction} < .05$), as shown in Table 5.

Discussion

Epidemiological investigations have shown that increased TC, TG, LDL-C, and ApoB levels and decreased HDL-C and ApoAI levels were independent risk factors for CHD.[8,9] Prospective intervention studies have found that reducing levels of TC, TGs, LDL-C, and ApoB, and increasing HDL-C and ApoAI levels can reduce the risk of atherosclerosis.[9] Our study found that after statin treatment, TC, TG, LDL-C, and ApoB levels decreased significantly, and ApoAI levels increased significantly; however, the HDL-C levels did not change significantly after treatment. At present, the guidelines in China recommend that the target LDL-C level should be less than 1.8 mmol/L for[3] very high-risk patients with arteriosclerotic cardiovascular disease (ASCVD). After an average of 9 months of lipid-lowering treatment in our study population, the average LDL-C level did not fully meet this standard. The data show that only 51 (32.1%) people met this standard. A recent study collected data on the status of target lipid attainment in high-risk patients with ASCVD with a history of myocardial infarction or revascularization in nearly 200 hospitals in China, and the results showed that 98% of these patients were treated with statins alone. Similar to our data, only 30% of them met the LDL-C standard.[10] The control of LDL-C by single-dose statin therapy for very high-risk patients with ASCVD is generally insufficient. It is suggested that we should strengthen lipid-lowering efforts in high-risk patients with ASCVD who still fail to meet the standard after treatment with conventional doses of statins.

HHcy is considered a new risk factor for atherosclerosis.[4,5] Folate deficiency is the main cause of HHcy because smoking, drinking, and cooked food dietary habits are common in China, which could lead to absorption disorders of folate and the loss of folate in food; however, folic acid supplementation is not popular in China, so folate, vitamin B6, and B12 deficiencies are not uncommon, resulting in a high proportion of HHcy in the Chinese population. In addition, methylene tetrahydrofolate reductase (MTHFR) is a key enzyme in Hcy metabolism, and the C677TT genotype is related to decreased MTHFR activity, reduced remethylation of Hcy to methionine, and an increased Hcy level.[11] In China, one-fourth of the population harbors the MTHFR C677T TT genotype, which is also an important factor leading to a high proportion of HHcy in China. In a recent study carried out by Chinese scholars, folic acid supplementation was shown to significantly reduce the risk of stroke in the hypertensive population in China, and the higher the level of Hcy was, the greater the benefit of folic acid supplementation.[4] Therefore, HHcy is considered to be a stronger key risk factor for cardiovascular and cerebrovascular diseases in the Chinese population than in the Western population, and lowering the Hcy level can confer greater cardiovascular benefits in the

Chinese population. Some studies have shown that statin therapy can reduce human Hcy levels in women with polycystic ovary syndrome,[6] renal transplant recipients,[12] and patients with hypercholesterolemia.[11] In the present study, we analyzed the changes in Hcy levels after atorvastatin treatment and found that the average level of Hcy decreased significantly (from 14.31 ± 5.96 μmol/L to 13.41 ± 5.04 μmol/L, $P < .05$). However, this association is not evident in some other studies.[13,14] To explain these controversies, we must understand that the effect of statins on Hcy was influenced by the baseline level of Hcy,[11] which was relatively high in our study, and that this would lead to the efficient therapy of atorvastatin, whereas in other studies, the baseline Hcy level was lower (approximately 10.5 μmol/L), and statin treatment was consequently less efficient. In addition, the effect of statins on Hcy was also influenced by the MTHFR C677T genotype, obesity,[11] and the study sample size, so the controversial results of different studies may be influenced by these factors. However, in a meta-analysis of 15 studies, statins indeed caused reductions (3.5%) in Hcy blood concentrations in a large sample.[15] The mechanism by which statins reduce Hcy levels in humans has not been fully studied. To the best of our knowledge, only Schroecksnadel et al[16] showed that statins may prevent Hcy accumulation in the blood via immunosuppression in vitro. Although the exact pathophysiological mechanisms underlying the association of the serum Hcy change with statin treatment remain to be further elucidated, in animal experiments, atorvastatin therapy can attenuate Hcy-induced reactive oxygen species accumulation and endothelial cell apoptosis through nicotinamide adenine dinucleotide phosphate oxidase and/or p38MAPK-dependent mechanisms.[17,18] Atorvastatin also inhibits Hcy-induced endothelium reticulum stress both in vitro and in vivo.[19] Kerstin Wustmann et al even showed that both statin and Hcy-lowering therapy (B-group vitamin supplementation) improved endothelial function in high-risk patients with cardiovascular disease but they act via different mechanisms.[20] Thus, atorvastatin may reduce inflammatory factors and oxidative stress by a reduction in Hcy levels or via mechanisms independent of Hcy to achieve antiatherosclerosis effects.

Recent clinical observations have shown a certain correlation between serum Hcy and blood lipid levels in patients with CHD.[21,22] The present study results also show a correlation between Hcy and blood lipid levels before atorvastatin treatment. When the statistical analysis was performed between normal Hcy and HHcy, the levels of serum TGs in the patients with HHcy were significantly higher than those in patients with normal Hcy, and the levels of serum HDL-C and ApoAI in patients with HHcy were significantly lower than those in patients with normal Hcy. Although we have not explored the mechanism of the relationship between Hcy and serum lipid levels (especially HDL-C and ApoAI), recent animal and in vitro cell studies have demonstrated that Hcy can suppress hepatic ApoAI expression via the peroxisome proliferator-activated receptor α-ApoAI pathway.[23] Moreover, Hcy could decrease the transcription of ApoAI by stimulating nuclear factor-κB and ApoAI regulatory protein 1 and[22] enhancing HDL-C clearance.[24] These increased Hcy levels may impair cardiovascular function via the reduction in HDL-C and the impairment of its antioxidant capacity.

Based on the effect of statins on lowering both blood lipids and Hcy and the relationship between Hcy and blood lipid levels, however, whether the lipid-lowering effect of atorvastatin and the reduction in Hcy exist independently or whether there is an interaction between them are still unclear. In the present study, we found that different changes in Hcy levels after statin treatment may lead to different lipid-lowering effects. According to the changes in Hcy, the patients were divided into 2 groups: the HE group and the HR group. The results showed that the Hcy level decreased in most patients (96 patients, 60.4%). A small proportion of patients still showed an upward trend (63 patients, 39.6%). When we further compared the lipid-lowering effect between the HE group and the HR group, we found that the 2 groups showed the same trend in decreasing TC, LDL-C, and ApoB levels and increasing ApoAI levels. In the HE group, the level of TGs after treatment was significantly higher than that before treatment ($P < .05$). In the HR group, the level of TGs after treatment was significantly lower than that before treatment ($P < .01$). The effect of atorvastatin on TG levels between the 2 groups showed an opposite trend. In the HE group, the level of HDL-C decreased after treatment ($P < .05$), and in the HR group, the level of HDL-C increased significantly after treatment ($P < .05$). Interestingly, the effect of atorvastatin on HDL-C levels between the 2 groups was significantly opposite ($P < .05$). As mentioned earlier, elevated serum TGs and decreased serum HDL-C levels are risk factors for CHD. These results suggest that after statin treatment, patients with decreased Hcy have more favorable blood lipid levels (increased HDL-C and decreased TGs), while patients with elevated Hcy have more harmful blood lipid levels (decreased HDL-C and increased TGs).

Current studies have shown that even in patients where LDL-C levels are up to standard, there is still a significant risk of macrovascular events and microvascular complications. The Treating to New Targets (TNT) study indicated that when stratified at different HDL-C levels, the incidence of cardiovascular events in patients with low levels of LDL-C was further reduced by 39% in the highest HDL-C level group compared with the lowest HDL-C level group.[25] It is suggested that even if the LDL-C level is up to standard, further increases in HDL-C levels can reduce cardiovascular events. Increased levels of TGs have been recognized as a risk factor for ASCVD and are often accompanied by decreased levels of HDL-C[8,9]; they are the main manifestations of metabolic syndrome and are the major risk factors for ASCVD.[26] Therefore, the possible cause of residual cardiovascular risk is closely related to whether statins reduce TGs and increase the level of HDL-C. Our study found that statins have more favorable lipid parameters in patients with reduced Hcy, suggesting that these patients may benefit from reduced Hcy levels by having a lower risk of residual cardiovascular events. However, our study is an observational study, and additional prospective randomized controlled trials are needed to confirm that statin treatment has

better lipid parameters and cardiovascular outcomes in patients with reduced Hcy than in patients with elevated Hcy.

Conclusion

The effects of atorvastatin on serum TGs and HDL-C levels depend on the changes in Hcy levels. Patients with decreased Hcy levels after atorvastatin treatment have more favorable lipid parameters. This finding suggests that in the treatment of ACS, we should not only strive to achieve the target LDL-C levels but also pay attention to the benefits of statin therapy in reducing Hcy levels.

Authors' Note

DFW participated in the design, collected the data and the samples, performed the statistical analyses, and drafted the manuscript. YXW and JLD conceived the study and participated in the design. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

This study was complied with the Declaration of Helsinki and approved by the Institutional Ethics Committee of People's Hospital of Guangxi Zhuang Autonomous Region. Written informed consent was obtained from the participants.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Natural Science Foundation of China (No:81660066), the Natural Science Foundation of Guangxi (No: 2016GXNSFBA380209), Guangxi Medical and Health Key Scientific Research Topics (No: 200959), Scientific Research and Technology Development Program of Guangxi (No:1598012-2), and the Self-Financing Problem of Guangxi Medical and Health (No: Z2016613; Z2016591).

ORCID iD

Dong-Feng Wu https://orcid.org/0000-0002-6479-6189

References

1. Liu S, Li Y, Zeng X, Wang H, et al. Burden of cardiovascular diseases in China, 1990-2016: findings from the 2016 global burden of disease study. *JAMA Cardiol*. 2019;4(4):342-352.
2. Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. *Metabolism*. 2007;56(11):1534-1541.
3. Joint Task Force for Guideline on the Assessment and Management of cardiovascular risk in China. Guideline on the assessment and management of cardiovascular risk in China [in Chinese]. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2019;53(1):13-35.
4. Huo Y, Li J, Qin X, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. *JAMA*. 2015;313(13):1325-1335.
5. Wang Y, Jin Y, Wang Y, et al. The effect of folic acid in patients with cardiovascular disease: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2019;98(37):e17095.
6. Kaya C, Cengiz SD, Berker B, Demirtas S, Cesur M, Erdogan G. Comparative effects of atorvastatin and simvastatin on the plasma total homocysteine levels in women with polycystic ovary syndrome: a prospective randomized study. *Fertil Steril*. 2009;92(2):635-642.
7. Momin M, Jia J, Fan F, et al. Relationship between plasma homocysteine level and lipid profiles in a community-based Chinese population. *Lipids Health Dis*. 2017;16(1):54.
8. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. the Framingham study. *JAMA*. 1986;256(20):2835-2838.
9. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation*. 1989;79(1):8-15.
10. Xing Y, Liu J, Hao Y, et al. Prehospital statin use and low-density lipoprotein cholesterol levels at admission in acute coronary syndrome patients with history of myocardial infarction or revascularization: Findings from the Improving Care for Cardiovascular Disease in China (CCC) project. *Am Heart J*. 2019;212:120-128.
11. Jiang S, Chen Q, Venners SA, et al. Effect of simvastatin on plasma homocysteine levels and its modification by MTHFR C677T polymorphism in Chinese patients with primary hyperlipidemia. *Cardiovasc Ther*. 2013;31(4):e27-3e23.
12. Monfared A, Azimi SZ, Kazemnezhad E. The association between atorvastatin administration and plasma total homocysteine levels in renal transplant recipients. *J Nephropathol*. 2016;5(3):98-104.
13. Milionis HJ, Papakostas J, Kakafika A, Chasiotis G, Seferiadis K, Elisaf MS. Comparative effects of atorvastatin, simvastatin, and fenofibrate on serum homocysteine levels in patients with primary hyperlipidemia. *J Clin Pharmacol*. 2003;43(8):825-830.
14. Dierkes J, Luley C, Westphal S. Effect of lipid-lowering and antihypertensive drugs on plasma homocysteine levels. *Vasc Health Risk Manag*. 2007;3(1):99-108.
15. Jankowski P, Kawecka-Jaszcz K. Lipid-lowering drugs and homocysteine. a comparison between statins and other lipid-lowering drugs. *Atherosclerosis*. 2004;172(1):191-194.
16. Schroecksnadel K, Frick B, Winkler C, Wirleitner B, Weiss G, Fuchs D. Atorvastatin suppresses homocysteine formation in stimulated human peripheral blood mononuclear cells. *Clin Chem Lab Med*. 2005;43(12):1373-1376.
17. Bao XM, Wu CF, Lu GP. Atorvastatin inhibits homocysteine-induced oxidative stress and apoptosis in endothelial progenitor cells involving Nox4 and p38MAPK. *Atherosclerosis*. 2010;210(1):114-121.
18. Bao XM, Wu CF, Lu GP. Atorvastatin attenuates homocysteine-induced apoptosis in human umbilical vein endothelial cells via inhibiting NADPH oxidase-related oxidative stress-triggered p38MAPK signaling. *Acta Pharmacol Sin*. 2009;30(10):1392-1398.

19. Jia F, Wu C, Chen Z, Lu G. Atorvastatin inhibits homocysteine-induced endoplasmic reticulum stress through activation of AMP-activated protein kinase. *Cardiovasc Ther*. 2012;30(6):317-325.
20. Wustmann K, Klaey M, Burow A, Shaw SG, Hess OM, Allemann Y. Additive effect of homocysteine- and cholesterol-lowering therapy on endothelium-dependent vasodilation in patients with cardiovascular disease. *Cardiovasc Ther*. 2012;30(5):277-286.
21. Xiao Y, Zhang Y, Lv X, et al. Relationship between lipid profiles and plasma total homocysteine, cysteine and the risk of coronary artery disease in coronary angiographic subjects. *Lipids Health Dis*. 2011;10:137.
22. Wang Y, Liu J, Jiang Y, Zhang H, Leng S, Wang G. Hyperhomocysteinemia is associated with decreased apolipoprotein AI levels in normal healthy people. *BMC Cardiovasc Disord*. 2016;16:10.
23. Mikael LG, Genest J Jr, Rozen R. Elevated homocysteine reduces apolipoprotein A-I expression in hyperhomocysteinemic mice and in males with coronary artery disease. *Circ Res* 2006;98: 564-571.
24. Liao D, Tan H, Hui R, et al. Hyperhomocysteinemia decreases circulating high-density lipoprotein by inhibiting apolipoprotein A-I Protein synthesis and enhancing HDL cholesterol clearance. *Circ Res*. 2006;99(6):598-606.
25. Barter P, Gotto AM, LaRosa JC, et al. Treating to new targets I: HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357(13):1301-1310.
26. Kwiterovich PO Jr. The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: a current review. *Am J Cardiol*. 2000;86(12A):5L-10L.