Original Article
Low-dose atorvastatin calcium combined with evolocumab: effect on regulatory proteins, lipid profiles, and cardiac function in coronary heart disease patients

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Abstract: Objective: To assess the effects of combining low-dose atorvastatin calcium with evolocumab on complement regulatory protein levels, lipid profiles, and cardiac function in patients with coronary heart disease (CHD). Methods: A prospective randomized controlled study was conducted, with 180 CHD patients enrolled from Guang'anmen Hospital, China Academy of Chinese Medical Sciences, and the Second Hospital of Shanxi Medical University between February 2022 and April 2023. These patients were randomly assigned to either the control group (n = 90), receiving low-dose atorvastatin calcium, or the research group (n = 90), receiving a combination of low-dose atorvastatin calcium and evolocumab. The changes in cardiac function indices, levels of blood lipids and complement proteins, incidence of side effects, and cardiovascular events were compared between the two groups. Results: After treatment, both groups exhibited reductions in blood lipid levels. However, the research group demonstrated significantly lower levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) compared to the control group (all P < 0.001). Additionally, improvements in cardiac function indices were observed in both groups, with the research group displaying greater enhancements in cardiac output (CO), stroke volume (SV), and left ventricular ejection fraction (LVEF). Furthermore, the levels of complement regulatory proteins, including CD45, CD46, CD55, and CD59, increased in both groups after treatment, with the research group exhibiting significantly higher levels (all P < 0.001). Notably, the research group also exhibited a lower incidence of cardiovascular events. Conclusion: The combined use of low-dose atorvastatin calcium and evolocumab effectively modulates complement regulatory protein levels, optimizes blood lipid profiles, and enhances cardiac function in patients with CHD. This combination therapy represents a promising approach for management of CHD.

Keywords: Low-dose atorvastatin calcium, evolocumab, coronary heart disease, complement regulatory protein, hyperlipidemia

Introduction

Coronary heart disease (CHD) arises when cardiac arteries narrow or become blocked, impeding the supply of oxygen-rich blood to the heart. According to the China Cardiovascular Health and Disease Report 2020, cardiovascular deaths are the leading cause of mortality among both urban and rural residents [1]. As the aging population increases, the incidence and mortality of CHD in China are projected to rise [2]. Epidemiological studies have identified elevated levels of low-density lipoprotein cholesterol (LDL-C) as the primary driver of atherosclerosis [3]. Reducing LDL-C levels has been associated with improved CHD outcomes [4]. A meta-analysis by the Cholesterol Treatment Collaborative Group in 2015 found that for every 1.0 mmol/L decrease in LDL-C, there was a 24% reduced risk of major coronary events and a 15% reduced risk of stroke [5]. For CHD treatment, the AHA emphasizes the significance

of healthy diets, regular exercise, and smoking cessation. In terms of drug therapy, traditional cholesterol-lowering drugs, antiplatelet agents, and hypoglycemic agents are prescribed, alongside newer drugs such as SGLT-2 inhibitors, GLP-1 receptor agonists, beta-blockers, bempedoic acid, and inclisiran. Hypercholesterolemia is a major contributor to CHD mortality, emphasizing the critical role of lipid control in CHD management. Statins remain the primary choice for lipid management, while PCSK9 inhibitors have also gained significant attention [6].

Statins occupy a pivotal position in lipid-lowering therapy. They enhance the expression of low-density lipoprotein receptor (LDLR) on the liver cell surface, promoting LDL cholesterol clearance from the bloodstream, thereby reducing plasma LDL cholesterol levels [7]. Statins have demonstrated their efficacy in reducing cardiovascular morbidity and mortality in both primary and secondary prevention settings [8]. Nevertheless, statins alone may not suffice for all patients. A significant proportion of patients, ranging from 7% to 29%, experience statin intolerance, manifesting as muscle pain and gastrointestinal issues [9]. Notably, Chinese patients often exhibit intolerance to high-dose statins. Therefore, the Chinese lipid management guidelines for 2023 [10] emphasize the use of combination therapy. This involves a moderate-intensity statin combined with a cholesterol uptake inhibitor. If LDL-C levels remain unattainable, a PCSK9 inhibitor can be added to the regimen. PCSK9, by binding to LDLR, degrades it, leading to elevated plasma LDL-C. Evolocumab, a monoclonal antibody, specifically binds to PCSK9, inhibiting its action. This blockade prevents PCSK9-mediated LDLR degradation, resulting in increased LDLR expression in hepatocytes [11]. Treatment experiences and in-depth studies on evolocumab have shown effective improvements in dyslipidemia-related indicators, with mild and tolerable adverse reactions [12]. Notably, the renowned FOURIER study demonstrated that patients treated with evolocumab had significantly lower risks of major adverse cardiovascular events compared to the placebo group [13].

Inflammation plays a pivotal role in CHD, undermining the stability of atherosclerotic plaques [14]. The complement system, a cornerstone of innate immunity, is vital in the inflammatory response. It can combat atherosclerosis by suppressing two key enzymes involved in complement activation and eliminating membrane attack complexes [15].

Despite studies exploring the treatment of CHD with low-dose atorvastatin calcium in combination with evolocumab, there are notable variations in trial design, observation metrics, sample selection criteria, and other factors. Additionally, as a monoclonal antibody, the immunological impacts of evolocumab are infrequently reported. Consequently, drawing a convincing and consistent conclusion remains challenging. Therefore, further research in this area is imperative.

Patients and methods

From February 2022 to April 2023, 180 CHD patients treated at Guang'anmen Hospital, China Academy of Chinese Medical Sciences, and Second Hospital of Shanxi Medical University were randomly allocated to a control group (n = 90) and a research group (n = 90). The control group received low-dose atorvastatin calcium, while the research group received additional evolocumab. Both groups underwent a one-month treatment course. Research flow chart is shown in **Figure 1**.

The diagnostic criteria for CHD adhered to the guidelines specified in "Guidelines for Primary Diagnosis and Treatment of Stable Coronary Heart Disease (2019 and 2020)" [16, 17].

Inclusion criteria: (1) patients had a confirmed diagnosis of CHD; (2) patients had no cognitive, linguistic, or intellectual impairment with basic literacy skills; (3) patients had no prior atorvastatin calcium or evolocumab treatment within the last month; (4) patients had no history of allergies to the study drugs; and (5) patients had excellent treatment compliance.

Exclusion criteria: (1) patients with severe liver insufficiency (glutamic pyruvic transaminase and glutamic oxaloacetic transaminase) levels exceeding 3 times the normal range or renal dysfunction (estimated glomerular filtration rate ≤ 30 ml/min/1.73 m²); (2) patients with other significant cardiovascular diseases, such as severe arrhythmia or cardiac insufficiency (left ventricular ejection fraction (LVEF) < 30%); (3) patients with other severe illnesses, including severe infection, thyroid disease,

Figure 1. Research flow chart. Note: CHD: Coronary Heart Disease.
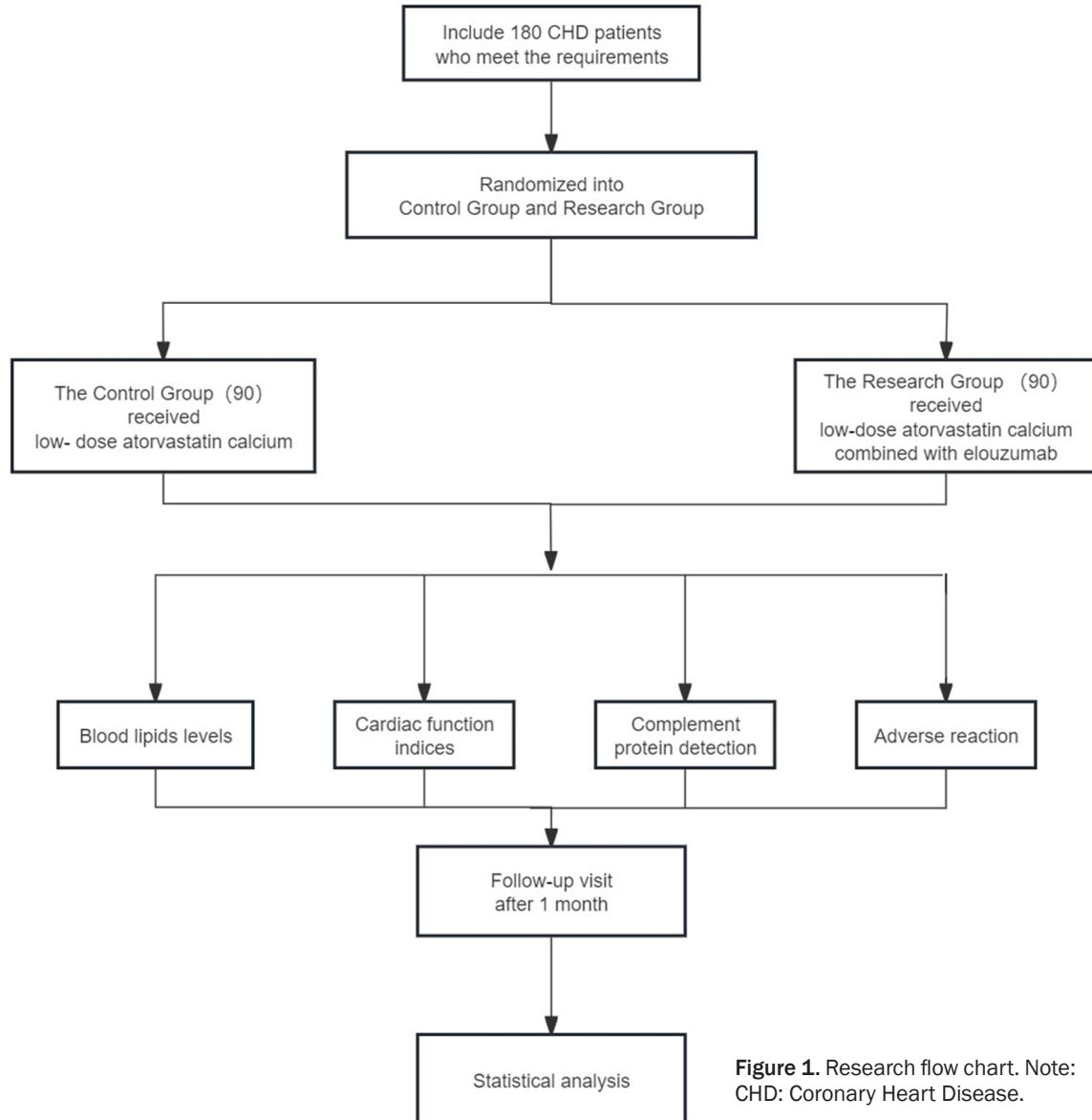
tuberculosis, or malignancy; and (4) patients with incomplete or missing clinical data.

This study received ethical approval from Guang'anmen Hospital, China Academy of Traditional Chinese Medicine and the Second Hospital of Shanxi Medical University (registration number: ChiCTR2200059379), and all patients provided informed consent as per the study requirements.

Immunohistochemistry treatment methods

In the control group, patients received low-dose atorvastatin calcium. Alongside routine administration of nitrates, calcium antagonists, β-receptor blockers, and antiplatelet drugs, pa-

tients were prescribed 10 mg atorvastatin calcium tablets (Pfizer Pharmaceutical Co., Ltd., approval number: H20051407) to be taken orally every night for a duration of one month.

The research group, in addition to the treatment received by the control group, underwent subcutaneous injection of evolocumab monoclonal antibody (140 mg/mL, Amgen Manufacturing Limited, imported drug registration number: S20180021) at a dose of 140 mg every two weeks for a total of one month.

Blood lipid levels

Blood lipid indices, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-

C), and triglycerides (TG), were compared before and one month after treatment. Patients were instructed to fast after 20:00 on the day prior to testing. On the test day, 5 ml of fasting venous blood was collected, and the serum was immediately separated by centrifugation (3000 rpm for 10 minutes). Once the centrifugation was complete, the inspector promptly aliquoted the serum samples into tubes designated for testing and transported them to the laboratory within 4-6 hours for analysis using a fully automated biochemical analyzer (MAGICL6800, Shanghai Jumu Medical Equipment Co., Ltd., approval number: Su Jie Zhi 20152221137). All inspections were conducted in strict accordance with the manufacturer's instructions and relevant regulatory procedures.

Fluctuation of cardiac function index

Cardiac function indices were compared before and one month following treatment. Echocardiography, utilizing the Philips EPIQ7C cardiac ultrasound diagnostic instrument (approval number: Guo Xie Jin 20193062262), was employed to assess changes in cardiac output (CO), stroke volume (SV), and LVEF.

Complement protein detection

Changes in complement regulatory proteins CD35, CD46, CD55, and CD59 on the surface of plasma and monocytes were observed pre-treatment and one month post-treatment. Fasting venous blood samples (2 ml) were collected into purple anticoagulant tubes. The median fluorescence intensity of CD35, CD46, CD55, and CD59 on monocytes was analyzed and calculated using flow cytometry. The BD Pharmingen kit (lot numbers: BD-Pharmingen 555451, BD-Pharmingen 555949, BD-Pharmingen 555691, BD-Pharmingen 555761) and BD FACS Calibur flow cytometry (lot number: BD FACS Calibur-342973) were utilized for these assays.

Adverse reactions and prognosis

The incidence of adverse reactions and adverse cardiovascular events was determined one month post-treatment. The total incidence of adverse reactions was calculated as the sum of all adverse reactions divided by the total number of cases, multiplied by 100%. Similarly, the incidence of adverse cardiovascular events was determined by dividing the total number of cardiovascular events by the total number of cases, multiplied by 100%. Abnormal creatinine refers to creatinine levels falling outside the normal range, typically 53-106 μmol/L for males and 44-97 μmol/L for females. Muscle soreness describes discomfort in muscles caused by various factors such as infection or exercise. Vertigo, a common brain functional disorder, is characterized by dizziness, a heavy sensation, and possibly visual disturbances, nausea, and vomiting. Gastrointestinal discomfort encompasses symptoms such as abdominal pain, bloating, nausea, vomiting, retching, and acid regurgitation. Recurrent angina pectoris refers to the reappearance of chest discomfort after treatment, often accompanied by other symptoms. Arrhythmia denotes irregularities in heart rate or rhythm resulting from abnormal electrical activity in the heart. Myocardial infarction occurs due to prolonged ischemia and hypoxia of the coronary arteries, leading to myocardial necrosis and typically presenting with severe and persistent chest pain. Heart failure is a condition in which the heart's ability to pump blood effectively is compromised, resulting in insufficient blood flow to meet the body's demands.

Statistical analysis

This study employed SPSS 21.0 statistical software for data analysis. Measured data were analyzed for normal distribution and variance homogeneity. Normally distributed or approximately normally distributed measurements were presented as mean ± standard deviation ($\overline{x}$±sd). Pairwise comparisons were conducted using paired t-tests, while independent sample t-tests were applied for separate group comparisons. Counted data were represented as n (%), and chi-square tests were utilized for analysis. Differences were considered significant at $P < 0.05$.

Results

General information

In the control group, patients ranged in age from 45 to 74 years, with 46 males and 44 females. The duration of CHD varied from 1 to 5 years, and body mass index (BMI) ranged from 17.45 to 27.79 kg/m^2.

Table 1. General information

Group	N	Age (years)	Sex		BMI (kg/m^2)	CHD Duration (years)
			Male	Female		
Control group	90	65.33±3.64	46	44	22.87±2.30	3.44±0.34
Research group	90	65.75±3.23	43	47	22.66±2.27	3.54±0.64
t/x^2		2.26	0.2		2.28	2.25
P		0.25	0.655		0.24	0.25

Note: CHD: Coronary Heart Disease; BMI: Body Mass Index.

Table 2. Blood lipid levels [±s, mmol/L]

Group	N	TC		TG		LDL-C	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	90	5.89±0.33	5.05±0.21[a]	1.83±0.34	1.69±0.25[a]	3.89±0.43	3.23±0.66[a]
Research group	90	5.81±0.54	4.14±0.34[a]	1.81±0.36	1.32±0.23[a]	3.81±0.49	2.84±0.34[a]
t		1.192	21.602	0.383	10.332	1.164	4.983
P		0.232	0.000[b]	0.702	0.000[b]	0.245	0.000[b]

Note: [a]compared to the same group before and after treatment. [b]$P < 0.001$. TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-density Lipoprotein Cholesterol.

The research group comprised patients aged 44 to 76 years, including 43 males and 47 females. CHD duration spanned 1 to 5.3 years, and BMI ranged from 17.31 to 27.84 kg/m^2. No significant differences were observed in baseline characteristics between the two groups.

Comparative analysis revealed no significant differences in sex, age, or duration of CHD between the groups (**Table 1**; all P > 0.05).

Comparison of blood lipid levels

Pretreatment blood lipid levels were comparable between the two groups, with no significant differences observed (P > 0.05). Post-treatment analysis revealed a decrease in TC, TG, and LDL-C in both groups, with significant differences (P < 0.001; **Table 2**; **Figure 2**).

Comparison of cardiac function indices

Both groups exhibited improved cardiac function indices following treatment. Notably, the research group demonstrated higher CO, SV, and LVEF compared to the control group (P < 0.001; **Table 3**; **Figure 3**).

Comparison of complement regulatory proteins

Post-treatment analysis revealed an elevation in complement regulatory proteins in both groups, as shown in **Figure 4**. The research group exhibited significantly higher levels of CD35, CD46, CD55, and CD59 compared to the control group (P < 0.001; **Table 4**; **Figure 5**).

Comparison of prognosis

While the control group exhibited a lower incidence of adverse reactions, no significant difference was observed between the groups (P > 0.05; **Table 5**). However, the research group demonstrated a significantly lower incidence of cardiovascular events compared to the control group (P < 0.001; **Table 6**).

Discussion

Multiple studies have demonstrated a strong association between elevated LDL-C levels and atherosclerosis [18]. This association is linked to the accumulation of cholesterol on the vascular wall, leading to plaque instability and the eventual rupture of lipid-rich plaques. Consequently, statins such as rosuvastatin and atorvastatin are widely prescribed for the treatment of hyperlipidemia [19]. Statins not only effectively lower blood lipid levels but also inhibit vascular endothelial inflammation, stabilize atherosclerotic plaques, improve endothelial function, and exhibit anti-thrombotic, anti-inflammatory, and neuroprotective effects. However, monotherapy with statins in patients
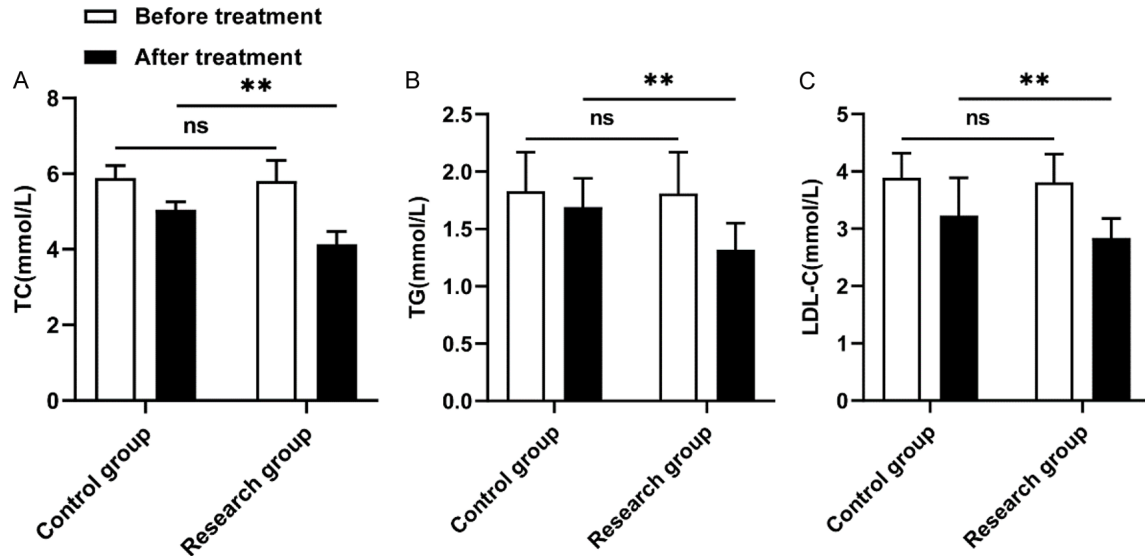
Figure 2. Blood lipid levels. Before treatment there was no significant difference in blood lipid levels (P > 0.05). The two groups showed significant differences in TC, TG and LDL-C after treatment (P < 0.001). A: Reduction in TC was observed in the study group after treatment; B: Reduction in TG was observed in the study group after treatment TG; C: Reduction in LDL-C was observed in the study group after treatment. Note: Compared to the same group before and after treatment, nsP > 0.05, **P < 0.001; TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-density Lipoprotein Cholesterol.

Table 3. Fluctuation in cardiac function indexes [±s, points]

Group	N	CO (L·min⁻¹)		SV (ml)		LVEF (%)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	90	3.79±0.31	4.01±0.33[a]	45.18±4.34	50.69±5.45[a]	40.19±5.34	43.19±3.32[a]
Research group	90	3.78±0.35	4.78±0.32[a]	45.19±4.41	55.69±5.34[a]	40.28±5.43	49.84±3.23[a]
t		0.202	15.891	0.015	6.216	0.112	13.619
P		0.839	0.000[b]	0.987	0.000[b]	0.910	0.000[b]

Note: [a]compared to the same group before and after treatment. [b]P < 0.001. CO: Cardiac Output; LVEF: Left Ventricular Ejection Fraction; SV: Stroke Volume.

with CHD often falls short of achieving the desired therapeutic outcome. Statin intolerance can significantly impact patients' treatment compliance and elevate the risk of cardiovascular events. Additionally, it may lead to complications such as liver function impairment and muscle soreness [20]. As a result, statins have certain limitations in the treatment of CHD.

Recently, PCSK9 inhibitors have emerged as a novel class of lipid-lowering drugs, with evolocumab gaining significant attention. Evolocumab was introduced in European medical clinics in 2015 and officially approved for use in China by the Drug Administration in 2018. This PCSK9 monoclonal antibody binds to PCSK9,

disrupting its interaction with the LDLR. By blocking this interaction, evolocumab prevents the LDLR's mediated degradation, effectively reducing LDL-C concentrations in the bloodstream. PCSK9 inhibitors can achieve a 50-70% greater reduction in LDL-C levels compared to statins alone [21].

In our study, both groups exhibited a reduction in blood lipid levels post-treatment. Notably, the research group demonstrated significantly lower levels of TC, TG, and LDL-C compared to the control group. This finding suggests that the addition of evolocumab to standard statin therapy may enhance the effectiveness of lipid-lowering treatment in patients with CHD.
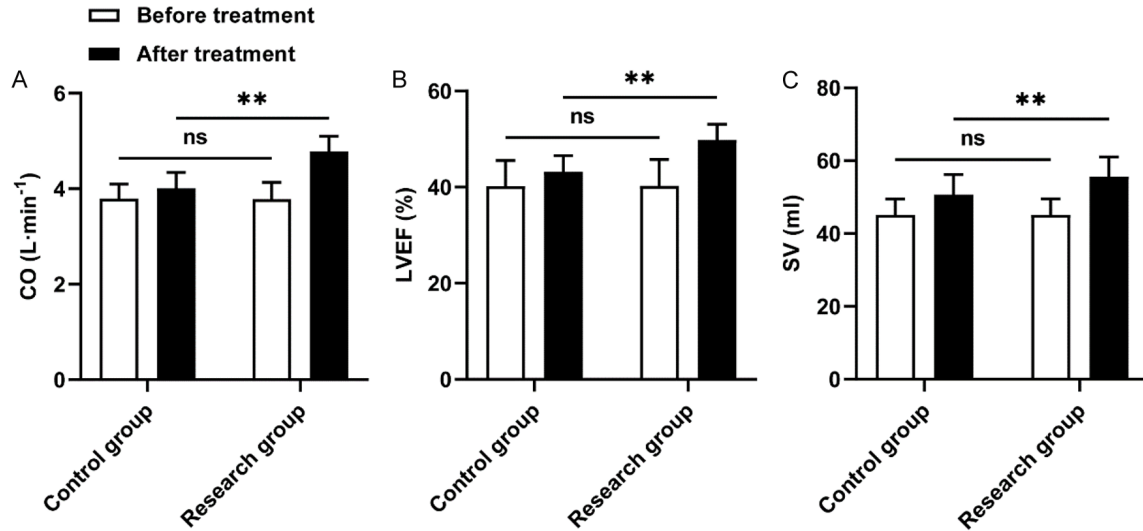
Figure 3. Fluctuation in cardiac function indices. Before treatment there was no significant difference in cardiac function indices (P > 0.05). The two groups showed significant differences in CO, LVEF, and SV after treatment (P < 0.001). A: Improvement in CO was observed in the study group after treatment; B: Improvement in LVEF was observed in the study group after treatment; C: Improvement in SV was observed in the study group after treatment. Note: Compared to the same group before and after treatment, nsP > 0.05, **P < 0.001; CO: Cardiac Output; LVEF: Left Ventricular Ejection Fraction; SV: Stroke Volume.
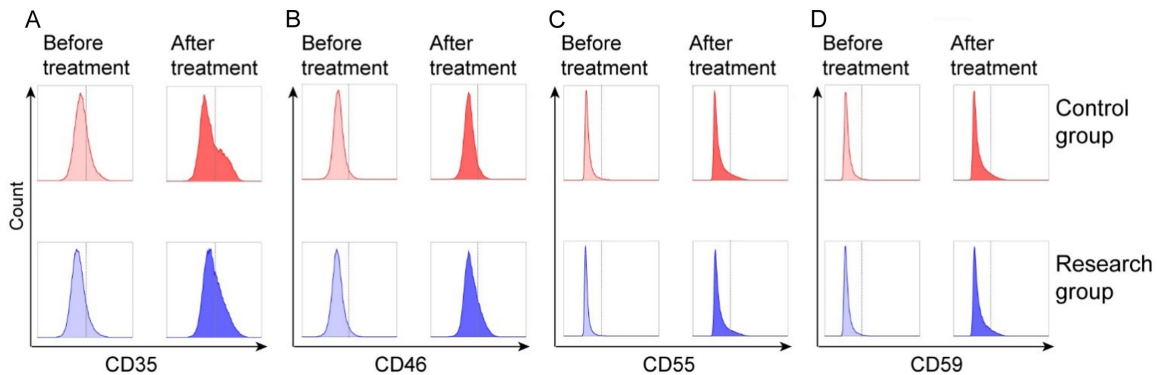

Figure 4. Levels of CD35, CD46, CD55, and CD59 in flow cytometry. The two groups showed significant differences in levels of CD35, CD46, CD55, and CD59 after treatment (P < 0.001). A: CD35 flow cytogram before and after treatment; B: CD46 flow cytogram before and after treatment; C: CD55 flow cytogram before and after treatment; D: CD59 flow cytogram before and after treatment.

Moreover, the research group exhibited higher levels of CO, SV, and LVEF, indicating a beneficial effect of evolocumab on enhancing cardiac function in CHD patients. Our findings revealed that evolocumab exhibited rapid effects, comparable to atorvastatin, in improving cardiac function. Notably, the follow-up data showed a significantly lower incidence of cardiovascular events in the research group compared to the control group. Therefore, evolocumab can effectively improve the short-term prognosis of CHD patients and reduce the risk of cardiovascular events by enhancing cardiac function.

The complement system, a widely distributed protein response network in the human body, plays a crucial role in fine-tuning physiological processes. In the pathogenesis of CHD, coronary atherosclerosis is central, involving lipid deposition, plaque rupture, and platelet aggregation, which are primarily influenced by monocytes and the complement system [19].

Table 4. Regulators of the complement system in both groups [±s, ng/ml]

Group	N	CD35		CD46	
		Before treatment	After treatment	Before treatment	Aftertreatment
Control group	90	68.49±5.45	89.38±5.44[a]	89.89±5.45	105.85±13.22[a]
Research group	90	68.89±5.64	99.75±5.45[a]	89.17±5.22	174.73±12.44[a]
t		0.483	12.775	0.905	35.997
P		0.629	0.000[b]	0.366	0.000[b]
Group	N	CD55		CD59	
		Before treatment	After treatment	Before treatment	Aftertreatment
Control group	90	7.49±5.34	10.48±2.32[a]	7.59±2.32	12.16±3.35[a]
Research group	90	7.29±5.43	15.93±4.23[a]	7.69±2.24	15.38±2.32[a]
t		0.249	10.716	0.294	7.496
P		0.803	0.000[b]	0.769	0.000[b]

Note: [a]compared to the same group before and after treatment. [b]$P < 0.001$.
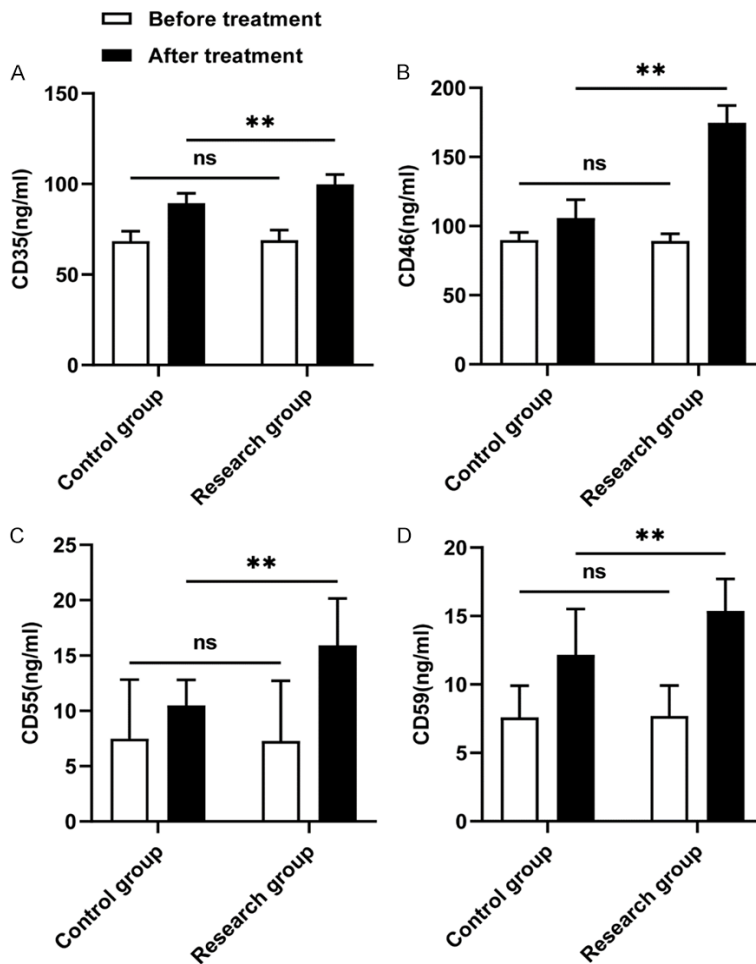

Figure 5. Complement regulatory proteins. Before treatment, there was no significant difference in cardiac function indices ($P > 0.05$). The two groups showed significant differences in CD35, CD46, CD55 and CD59 after treatment ($P < 0.001$). A: Higher level of CD35 was observed in the study group after treatment; B: Higher level of CD46 in the study group after treatment; C: Higher level of CD55 in the study group after treatment; D: Higher level of CD59 in the study group after treatment. Note: Compared to the same group before and after treatment, nsP > 0.05, **P < 0.001.

Activation of the complement system releases inflammatory complexes that stimulate the activity of endothelial cells, monocytes, and platelets, leading to the release of inflammatory factors and complexes. These factors further promote the proliferation and migration of smooth muscle cells. Consequently, the complement system plays a pivotal role in the development of CHD.

Complement regulatory proteins, present in both plasma and on cell membranes, control the intensity and scope of complement system activation by inhibiting crucial enzymes in the activation pathway [22]. CD35, a complement adhesion receptor, binds to active complement fragments, rendering them inactive [23]. CD46 acts as an accessory protein, facilitating the degradation of active complement fragments [24]. CD55 functions as a complement decay-promoting factor, reducing complement activity and preventing C3b and C4b from serving as core components in the formation of C3 and C5 convertases [25]. These three pro-

Table 5. Incidence of adverse reactions [n/%]

Group	N	Creatinine abnormality	Muscle soreness	Vertigo	Gastrointestinal discomfort	Incidence of adverse reactions
Control group	90	1 (1.11)	1 (1.11)	1 (1.11)	2 (2.22)	6 (5.56)
Research group	90	0 (0.00)	1 (1.11)	0 (0.00)	0 (0.00)	1 (1.11)
χ^2				2.378		
P				0.123		

Table 6. Incidence of adverse cardiovascular events [n/%]

Group	N	Recurrent angina pectoris	Arrhythmia	Myocardial infarction	Heart failure	Total
Control group	90	5 (5.56)	6 (6.67)	0 (0.00)	2 (2.22)	13 (14.44)
Research group	90	1 (1.11)	2 (2.22)	0 (0.00)	0 (0.00)	3 (3.33)
χ^2			5.556			
P			0.018			

teins play a negative regulatory role, blocking the function of C3 and C5 enzymes, ultimately deactivating them and slowing down complement activation. This facilitates the clearance and transportation of immune substances generated in the body's circulation [26]. CD59, as a membrane-reactive lytic inhibitor, prevents the active component C9 from entering the cell membrane, thus hindering the formation of membrane-attacking complexes in the final stages of complement activation and safeguarding cells from lysis [27].

In this study, the levels of CD45, CD46, CD55, and CD59 significantly increased following therapeutic intervention, with a more pronounced elevation observed in the research group compared to the control group. These proteins are well-established inhibitors of C3 and C5 convertase synthesis, suppressing the cascade reaction of complement activation at critical points of C3 and C5. This suppression prevents the generation of downstream inflammatory mediators and membrane attack complexes, safeguarding the host from inflammatory damage triggered by complement activation. A prior study comparing LDL apheresis with the PCSK9 inhibitor evolocumab found that LDL reduction significantly activated the alternative complement system, whereas PCSK9 inhibitors had no such effect, thereby averting the subsequent cascade response [28]. Additionally, in vitro experiments have demonstrated that low-dose atorvastatin calcium combined with evolocumab can enhance the expression of CD55 and CD59 on vascular endothelium, possibly linked to its lipid-regulating and plaque-stabilizing

actions. Furthermore, evolocumab has been shown to promote the upregulation of CD35 on monocyte surfaces, conferring an anti-atherosclerotic effect [29]. This evidence supports our conclusion that the combination of low-dose atorvastatin calcium and evolocumab can elevate the expression of complement regulatory proteins, effectively suppressing complement-mediated inflammation.

The intricate relationship between complement, blood lipids, and heart function demands further exploration. First, the complement system serves as a crucial factor in lipid metabolism and is intricately involved in lipid-rich deposit diseases [30]. Abnormalities in lipid metabolism are directly associated with cardiomyocyte damage, as oxidized lipids trigger various metabolic and functional disturbances within cells, ultimately leading to cellular apoptosis. Notably, a study revealed that the cytotoxic effects of oxidized lipids are exacerbated in obese individuals, thereby affecting cardiac function [31]. Second, the activation of the complement system contributes to the destruction of the cardiac endothelium. This activation triggers immunoadhesive, chemotactic, and direct inflammatory effects, causing damage to the vessel wall. Additionally, LDL interacts with the complement, further intensifying the damage to the vascular endothelium and smooth muscle. Lastly, the activation of the complement system also affects cardiomyocytes, leading to their damage. This cardiomyocyte damage serves as a crucial determinant of decreased cardiac function. Evidence suggests that the C5aR signaling pathway in blood mono-

cytes/macrophages plays a pathologic role in Ang II-induced cardiac inflammation and re-modeling [32]. Similarly, another study directly implicated the C3-C5aR-C3aR pathway in the pathogenesis of right ventricular failure [33]. In summary, modulating the complement system presents a promising therapeutic avenue for improving cardiac function by mitigating its abnormal effects on lipid metabolism, reducing cardiomyocyte damage, and alleviating inflammatory damage to the cardiac vasculature.

The study's limitations include the absence of long-term follow-up on patient prognosis and the specific inter-relationships between complement, lipids, and cardiac function. Due to the small sample size, future research should use cross-regional, multi-center studies with larger cohorts to achieve a more precise and comprehensive understanding of these intricate relationships.

Conclusion

Combined use of low-dose atorvastatin calcium and evolocumab in CHD treatment effectively modulates complement regulatory protein levels, reduces blood lipid concentrations, and enhances cardiac function, while maintaining high therapeutic safety. This therapeutic approach offers a promising strategy for CHD management.

Acknowledgements

Disclosure of conflict of interest

None.

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References

[1] Katta N, Loethen T, Lavie CJ and Alpert MA. Obesity and coronary heart disease: epidemi-ology, pathology, and coronary artery imaging. Curr Probl Cardiol 2021; 46: 100655.

[2] Kopparam RV, Grady D and Redberg RF. Coronary heart disease testing before kidney transplant-a call for revised guidance. JAMA Intern Med 2023; 183: 287-288.

[3] Simonetto C, Rospleszcz S, Kaiser JC and Furukawa K. Heterogeneity in coronary heart disease risk. Sci Rep 2022; 12: 10131.

[4] Arenas de Larriva AP, Limia-Pérez L, Alcalá-Díaz JF, Alonso A, López-Miranda J and Delga-do-Lista J. Ceruloplasmin and coronary heart disease-a systematic review. Nutrients 2020; 12: 3219.

[5] Venkatachalam A, Levy J, Perolini S, Vignaux L and Mounier-Vehier C. Acute coronary heart disease and women. Rev Med Suisse 2022; 18: 1664-1669.

[6] Virani SS, Newby LK, Arnold SV, Bittner V, Brewer LC, Demeter SH, Dixon DL, Fearon WF, Hess B, Johnson HM, Kazi DS, Kolte D, Kumbhani DJ, LoFaso J, Mahtta D, Mark DB, Minissian M, Navar AM, Patel AR, Piano MR, Rodriguez F, Talbot AW, Taqueti VR, Thomas RJ, van Diepen S, Wiggins B and Williams MS; Peer Review Committee Members. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on clinical practice guidelines. Circulation 2023; 148: e9-e119.

[7] Abdelatif N, Peer N and Manda SO. National prevalence of coronary heart disease and stroke in South Africa from 1990-2017: a systematic review and meta-analysis. Cardiovasc J Afr 2021; 32: 156-160.

[8] Hasbani NR, Ligthart S, Brown MR, Heath AS, Bebo A, Ashley KE, Boerwinkle E, Morrison AC, Folsom AR, Aguilar D and de Vries PS. American Heart Association's life's simple 7: lifestyle recommendations, polygenic risk, and lifetime risk of coronary heart disease. Circulation 2022; 145: 808-818.

[9] Dumler S, Krötz F and Siegmund T. Which anti-diabetic drugs im prove coronary heart disease and heart failure? MMW Fortschr Med 2021; 163: 42-46.

[10] Joint Expert Committee on Revision of Chinese Lipid Management Guidelines. Chinese lipid management guidelines (2023). Chin J Cardiol 2023; 51: 221-255.

[11] Saud A, Ali N, Gali F, Qassam H and Hadi NR. The effect of evolocumab alone and in combination with atorvastatin on atherosclerosis progression and TLRs expression. J Med Life 2023; 16: 759-765.

[12] Abdul-Rahman T, Bukhari SMA, Herrera EC, Awuah WA, Lawrence J, de Andrade H, Patel N,

Shah R, Shaikh R, Capriles CAA, Ulusan S, Ahmad S, Corriero AC, Mares AC, Goel A, Hajra A, Bandyopadhyay D and Gupta R. Lipid lowering therapy: an era beyond statins. Curr Probl Cardiol 2022; 47: 101342.

[13] Bonaca MP and Sabatine MS. Response by bonaca and sabatine to letters regarding article, "low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk)". Circulation 2018; 138: 222-223.

[14] Voutilainen A, Brester C, Kolehmainen M and Tuomainen TP. Epidemiological analysis of coronary heart disease and its main risk factors: are their associations multiplicative, additive, or interactive? Ann Med 2022; 54: 1500-1510.

[15] Correale M and Brunetti ND. Alcohol consumption and subclinical and clinical coronary heart disease: new insight into potential causal mechanisms. Eur J Prev Cardiol 2022; 29: 2003-2005.

[16] Chinese Medical Association, Journal of Chinese Medical Association and General Practice Branch of Chinese Medical Association. Guidelines for stable primary diagnosis and treatment of coronary heart disease (2020). Chin J Gen Pract 2021; 20: 265-273.

[17] Chinese Medical Association, Journal of Chinese Medical Association and General Practice Branch of Chinese Medical Association, et al. Guidelines for the primary diagnosis and treatment of dyslipidemia (2019). Chin J Gen Pract 2019; 18: 406-416.

[18] Lippi G, Cervellin G and Sanchis-Gomar F. Prognostic value of troponins in patients with or without coronary heart disease: is it dependent on structure and biology? Heart Lung Circ 2020; 29: 324-330.

[19] Hidayat K, Chen JS, Wang HP, Wang TC, Liu YJ, Zhang XY, Rao CP, Zhang JW and Qin LQ. Is replacing red meat with other protein sources associated with lower risks of coronary heart disease and all-cause mortality? A meta-analysis of prospective studies. Nutr Rev 2022; 80: 1959-1973.

[20] Nebel R. Exercise in coronary heart disease (CHD) - Prognostic relevance of physical activity and training. MMW Fortschr Med 2020; 162: 36-40.

[21] Infante T, Del Viscovo L, De Rimini ML, Padula S, Caso P and Napoli C. Network medicine: a clinical approach for precision medicine and personalized therapy in coronary heart disease. J Atheroscler Thromb 2020; 27: 279-302.

[22] Ripley DP, Jenkins NP and Thomas HE. The use of adenosine in the assessment of stable coronary heart disease. J R Coll Physicians Edinb 2019; 49: 182-184.

[23] Chen Z, Koralov SB and Kelsoe G. Regulation of humoral immune responses by CD21/CD35. Immunol Rev 2000; 176: 194-204.

[24] Mishra N, Mohata M, Narang R, Lakshmy R, Hazarika A, Pandey RM, Das N and Luthra K. Altered expression of complement regulatory proteins CD35, CD46, CD55, and CD59 on leukocyte subsets in individuals suffering from coronary artery disease. Front Immunol 2019; 10: 2072.

[25] Pothineni NVK, Rochlani Y, Subramany S, Kovelamudi S and Mehta JL. Hepatic interactions in atherosclerotic heart disease. Am J Med Sci 2022; 363: 104-113.

[26] Chauhdary WA, Rubel AR, Bashir A, Hla Aye MT, Javed N, Soe ZN, Sharif SMA, Mani BI, Oomen M and Chong VH. Earlobe crease (Frank's sign) and coronary heart disease. QJM 2020; 113: 902.

[27] Kokubo Y, Watanabe M, Higashiyama A and Honda-Kohmo K. Small-dense low-density lipoprotein cholesterol: a subclinical marker for the primary prevention of coronary heart disease. J Atheroscler Thromb 2020; 27: 641-643.

[28] Lappegård KT, Enebakk T, Thunhaug H, Ludviksen JK, Mollnes TE and Hovland A. LDL apheresis activates the complement system and the cytokine network, whereas PCSK9 inhibition with evolocumab induces no inflammatory response. J Clin Lipidol 2016; 10: 1481-1487.

[29] Dimopoulos MA, Dytfeld D, Grosicki S, Moreau P, Takezako N, Hori M, Leleu X, LeBlanc R, Suzuki K, Raab MS, Richardson PG, Popa McKiver M, Jou YM, Yao D, Das P and San-Miguel J. Elotuzumab plus pomalidomide and dexamethasone for relapsed/refractory multiple myeloma: final overall survival analysis from the randomized phase II ELOQUENT-3 trial. J Clin Oncol 2023; 41: 568-578.

[30] Moreno-Navarrete JM, Martínez-Barricarte R, Catalán V, Sabater M, Gómez-Ambrosi J, Ortega FJ, Ricart W, Blüher M, Frühbeck G, Rodríguez de Cordoba S and Fernández-Real JM. Complement factor H is expressed in adipose tissue in association with insulin resistance. Diabetes 2010; 59: 200-209.

[31] Hajri T. Effects of oxidized lipids and lipoproteins on cardiac function. Front Biosci (Landmark Ed) 2018; 23: 1822-1847.

[32] Zhang C, Li Y, Wang C, Wu Y, Cui W, Miwa T, Sato S, Li H, Song WC and Du J. Complement 5a receptor mediates angiotensin II-induced cardiac inflammation and remodeling. Arterioscler Thromb Vasc Biol 2014; 34: 1240-1248.

[33] Ito S, Hashimoto H, Yamakawa H, Kusumoto D, Akiba Y, Nakamura T, Momoi M, Komuro J, Katsuki T, Kimura M, Kishino Y, Kashimura S, Kunitomi A, Lachmann M, Shimojima M, Yozu G, Motoda C, Seki T, Yamamoto T, Shinya Y, Hiraide T, Kataoka M, Kawakami T, Suzuki K, Ito K, Yada H, Abe M, Osaka M, Tsuru H, Yoshida M, Sakimura K, Fukumoto Y, Yuzaki M, Fukuda K and Yuasa S. The complement C3-complement factor D-C3a receptor signalling axis regulates cardiac remodelling in right ventricular failure. Nat Commun 2022; 13: 5409.